The Evaluation of the Uraemic Heart using Cardiovascular Magnetic Resonance Imaging

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Abstract

Cardiovascular disease (CVD) accounts for over 50% of morbidity and mortality in patients with end stage renal failure (ESRF), including those suitable for renal transplantation. Furthermore, CVD is the most common cause for loss of a functioning renal allograft. The strongest predictors of cardiovascular (CV) outcome in this population have been identified as left ventricular (LV) abnormalities, namely left ventricular hypertrophy (LVH), left ventricular dilation (LVDil) and left ventricular systolic dysfunction (LVSD). However, inaccuracies inherent to the measurement of LV mass and volumes using echocardiography have meant that, unlike other populations such as those with essential hypertension, there is no reliable, consistent evidence that regression of LV abnormalities is possible or whether regression of LV abnormalities improves long term outcome.

Cardiovascular magnetic resonance (CMR) imaging is now established as the standard of reference for the measurement of LV mass, volumes and function, and unlike echocardiography is 'loading independent'. The aim of this thesis is to evaluate the uraemic heart using CMR, identify the determinants of LV abnormalities and define the relationship between coronary artery disease (CAD) and LV abnormalities in a population of patients with ESRF felt suitable for renal transplantation.

Methods

A total of 154 patients with ESRF who were either already awaiting renal transplantation or undergoing assessment for transplantation were recruited for the study. Patients underwent the standard CV risk assessment used by the West of Scotland transplant

assessment clinic and in addition underwent CMR imaging and measurement of serum brain natriuretic peptide (BNP). A proportion of patients (60) also underwent an additional CMR protocol using a gadolinium based contrast agent and 84 patients returned after a mean period of 8 months for a follow-up CMR scan to study the natural history of LV abnormalities whilst patients await renal transplantation.

Results

In contrast to previous echocardiographic studies, rather than three types of uraemic cardiomyopathy, namely concentric LVH, eccentric LVH and LVSD, the results of this study suggest only two major types of uraemic cardiomyopathy exist; concentric LVH and ischaemic cardiomyopathy (ICM). The predominant type of cardiomyopathy was concentric LVH, which was associated with hypertension and diabetes and 50% of the total cohort were found to have this type of cardiomyopathy. Thereafter, LVDil was found to be associated with LVSD in the majority of cases and patients with LVDil and/or LVSD were much more likely to have associated CAD than patients with either normal ventricles or concentric LVH. Only a very small proportion of the total cohort was found to have eccentric LVH (6%) when a loading independent method of measurement was used for the assessment of LV abnormalities.

With follow-up, 45% patients who were found to have an initially normal LV developed concentric LVH, whilst patients with an initially abnormal LV showed little further progression during the study period. Patients with LVSD or LVDil had a poorer outcome than those with concentric LVH or normal ventricles after 4 years of follow-up and patients who displayed contrast enhancement after administration of a gadolinium based

contrast agent, indicative of myocardial necrosis/fibrosis also had a significantly poorer outcome compared to those with no evidence of contrast enhancement.

Age, a prior history of ischaemic heart disease (IHD) or diabetes and an elevated BNP level were all found to be independent predictors of all cause mortality in this population after 4 years of follow-up.

Conclusions

LV abnormalities are common in patients with ESRF awaiting renal transplantation. The two major types of cardiomyopathy in this population, identified using CMR, are concentric hypertrophic cardiomyopathy and ICM. Concentric hypertrophic cardiomyopathy, which is the most prevalent type of cardiomyopathy, is determined by hypertension, diabetes and volume overload and future studies targeting regression of LVH in this population should concentrate on treatment in these areas. LVSD and LVDil are under recognised in this population and both abnormalities are closely associated with CAD. A finding of either LVSD or LVDil should precipitate careful investigation for underlying CAD and strategies for the early non-invasive detection of CAD, before the development of ICM, in this population are required.

The mortality rate of patients awaiting renal transplantation remains high and is dependent on age, diabetes and IHD. In addition to established methods of CV risk stratification prior to renal transplantation, BNP level may prove to be a useful non-invasive marker of CV risk assessment in this population and further studies are warranted in parallel with those targeting LV abnormalities and CAD.

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The remainder of the work was carried out by me and the writing of this thesis was entirely my own work.

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Chapter 1

Introduction

1.1 The scale of the problem of Cardiovascular Disease in patients with Chronic Renal Failure

Renal transplantation, along with advances in immunosuppressive drug regimens and improved access to renal replacement therapy (RRT) has significantly improved the survival of patients with progressive renal failure (1-5). These improvements in survival, in combination with an aging population have resulted in an expansion of dialysis programmes in the United Kingdom (UK). In Scotland, the number of patients commencing dialysis increased from 60 patients per million (PPM) in 1989 to 108 PPM in 1999 (6) and the total number of patients in a dialysis programme in Scotland in 2006 was 2146 (an increase of 400 patients over 6 years) (7). This translates into a higher number of patients undergoing assessment for renal transplantation and being placed on renal transplant waiting lists. In 1996, there were 4322 patients on an active renal transplant waiting list in the UK and by 2005 this number had progressively increased to 5863 patients (8). However, this increase in demand has not been matched with a similar increase in supply of donor kidneys. In the UK, 1578 renal transplants were carried out in 1996, whereas only 1324 transplants were performed in 2005. This decrease in transplant activity reflects a drop in the number of donors, from 822 in 1996, to 721 in 2005 (8), felt to be due to a decrease in the number of deaths due to road traffic accidents and subarachnoid haemorrhage amongst other factors.

Renal transplantation is the most successful and cost effective treatment for renal failure. Not all patients on dialysis are suitable for transplantation and there is a variation in selection criteria, both between different renal units within the UK (9) and between different countries (10). In Scotland, 38% patients entering dialysis programmes are placed on the renal transplant waiting list (11) and studies have confirmed that renal transplantation significantly increases the life expectancy of patients with ESRF compared to those who remain on the transplant waiting list (1,3).

As the number of patients on waiting lists increases, the average length of time spent on the list before undergoing transplantation also increases. Until recently, it was thought that a longer wait for renal transplant impacted negatively on the morbidity and mortality benefit gained by transplantation. However, more recent evidence suggests that individual benefit from transplantation does not diminish with an increased length of waiting time, but instead is associated with a lower relative risk of death compared with remaining on dialysis (12). Patients left on the waiting list have a higher rate of mortality and with progression of time those patients remaining on the waiting list are those with less co-morbidity, who gain a similar benefit from transplantation as those who were transplanted earlier.

Thus it is realised, that to maximise the benefit of renal transplantation, rather than rationing access to the waiting list, when individual benefit of transplant can increase life expectancy by up to three times that of remaining on RRT, emphasis should be placed on improving outcome in patients awaiting renal transplant and in the first post transplant year (12).

The success of renal transplantation and improved survival on RRT has uncovered a greatly increased risk of CVD in this population (13-17). It is now well recognised that mortality from CV causes is higher in patients from the earliest stages of chronic renal failure (CRF) compared to the general population (18-19) but dramatically increases in patients with ESRF. In patients on RRT, CVD is responsible for over one third of hospitalization (14) and 50% of deaths are due to CV causes (14-15,17,20).

Statistics from the United States Renal Data Service (USRDS) estimates the mortality from CVD in patients on RRT in America is 10% per year, which is 30 times higher than that of the general population (14). After stratification for age and sex, the mortality from CVD remains 10-20 times higher (Graph 1.1) (17) and in patients with ESRF due to diabetic nephropathy the mortality from CVD is up to 50 times that of the general population. This increased risk is relatively higher in younger age groups, such that a 25 year old on RRT has the same CV risk as a patient of 85 years old in the general population (Graph 1.1).

Due to the selection bias of patients who are placed on renal transplant waiting lists, the mortality rate in this subset of patients is significantly lower than that of other patients on RRT (1,3) but death from CV causes still accounts for the majority of deaths and this subset of patients are 10 times more likely to die of CV causes than those in the general population (1). In the immediate period post renal transplant, acute myocardial infarction (AMI) and/or sudden arrhythmic death are major reasons for patient morbidity and mortality (13) and longitudinal studies of patients placed on renal transplant waiting lists show a sharp increase in mortality at time of transplant, to higher than that of those remaining on the waiting list (1,3, 12-13). Over the first 12 months post transplantation,

the mortality rate in patients with a functioning allograft significantly falls to below that of remaining on RRT but patients remain at 5 times greater CV risk compared to patients in the general population and CV death is the most common cause of loss of a functioning renal allograft.

Thus CVD is the major cause of morbidity and mortality at all stages of progressive renal failure, accounting for over 50% of deaths and is the primary reason for loss of an otherwise functioning renal allograft. It is therefore clear that to further improve the survival of patients with renal failure both before and after renal transplantation and to maximise the survival benefits of the limited number of donor kidneys available in the UK, improvements in both the detection and treatment of underlying CV disease in patients with renal failure are required.

1.2 The Natural History of Cardiovascular Disease in patients with Chronic Renal Failure

With improvements in survival and longevity in the general population, the incidence of CRF is rising and is reflected in part, in the increased number of patients entering dialysis programmes. However, the proportion of patients commencing RRT and ultimately undergoing renal transplantation is much smaller than the proportion of patients with CRF in the general population (21). In America it is estimated that whilst 0.1% of the population have ESRF, 10% have CRF. Therefore, the majority of patients with CRF die before ever reaching ESRF and these patients are over 20 times more likely to die from CV causes than entering a dialysis programme (22).

There are few large prospective studies examining the incidence of CVD in patients with CRF not requiring dialysis, without CVD at baseline. Jungers *et al.* (18) followed 147

patients with a glomerular filtration rate (GFR) of between 20-50ml/min/1.73m^2 and no history of CVD for 10 years. The study found the incidence of CV events to be 41% in men and 19% in women. The incidence of AMI was 3 times higher in men than that of the general population in all age groups and similar differences were observed for women up until the age of 65 when the difference became less marked.

The degree of CV risk seems to increase as GFR declines. In the ARIC study (19), the incidence of de novo CV events was 4.8% per year for patients with stage 2 CRF (GFR 60-89ml/min) but was 9.3% per year in those with stage 3-4 CRF (GFR 15-59ml/min). Similarly, in a cohort of 6223 patients in the Framingham study (22), 18% of men and 20% of women with renal impairment had CVD. The incidence rate of CV events was 23.1/1000 patient years for men and 25.6/1000 patient years for women with stage 3 CRF (GFR 30-59ml/min), whereas the corresponding rates for patients with stage 2 CRF were 18.5/1000 patient years and 11.0/1000 patient years respectively.

The prevalence of CAD and 'congestive' heart failure (CHF) is also higher in patients with CRF compared to those in the general population. Levin *et al.* (23) found a prevalence of CAD of 14.9% in patients with a GFR of <60ml/min and a prevalence of CHF of 7.2%. Conversely, in patients presenting with acute coronary syndromes (ACS) up to 33% have stage 3 or greater CRF (24).

Once patients reach ESRF and require dialysis, CV risk dramatically increases compared to both the general population and those in the earlier stages of progressive renal failure and it has been estimated that men over 60 commencing RRT have a poorer 5 year survival than men with colon cancer and women over 60 commencing RRT have a poorer outcome than women with breast cancer (14). The prevalence of IHD in patients

commencing RRT differs according to geographical location. In the US, 41% of patients have IHD (25), whereas in Australia and New Zealand the prevalence is 36% (26) and in Canada, 28% (14). In the UK, Metcalfe *et al.* (27) studied 523 patients who started dialysis in Scotland between 1998 and 1999 and found that 29% of patients had a history of IHD. In another study by Barrett *et al.* (28) of 822 patients commencing RRT, 18% of patients had had a previous AMI and 21% had a history of IHD. This in part, may be explained by the relatively high proportion of patients entering dialysis programmes with diabetes. In America, around 40% of patients commencing RRT are diabetic, whereas in Canada the proportion is lower at 29% and in the study of Metcalfe *et al.* 24% of patients in Scotland commencing RRT were diabetic. The high proportion of patients with IHD and/or diabetes is also reflected in a relatively high prevalence of other forms of vascular disease, namely peripheral vascular disease (PVD) and cerebrovascular disease (CBD), which is estimated at 17% and 5% respectively in patients commencing RRT (28).

CHF is also prevalent in patients commencing RRT. Heart failure in patients with advanced renal failure is usually defined clinically as typical symptoms of breathlessness and oedema and the clinical findings of bibasal crackles on chest auscultation. Therefore, volume overload could also be responsible for symptoms of CHF in patients with CRF, rather than primary myocardial dysfunction and in practice the two are often found in combination. In the US, 40% of patients on RRT have a history of CHF (14) whereas in the Canadian study of Barrett *et al.* 35% of patients had a prior history of CHF (28). Despite this clinical definition of CHF, the presence of the typical symptoms confers worsened prognosis. Patients commencing RRT with symptoms of CHF are 93% more likely to die than those commencing RRT with no such symptoms (29). Similarly, those

starting dialysis with a history of IHD, also usually symptom defined, have a 48% higher rate of mortality than patients commencing RRT with no prior history of IHD (30).

Once established on RRT, a high incidence of new onset IHD and CHF further contributes to the burden of CVD. In a Canadian study by Churchill *et al.* (31) the incidence of AMI was 8.2% per year and 10% per year for CHF. Longitudinal studies of patients on dialysis with no initial history of IHD or CHF have found that the development of de novo IHD and CHF is 3.6% per year (29) and 7.6% per year (30) respectively. With an already high prevalence of CVD in patients commencing RRT and the continued development of both IHD and CHF once established on RRT, it is unsurprising that 50% of patients on dialysis die of CV causes. In the study of Metcalfe *et al.* after 2 years follow up of 523 patients commencing RRT in Scotland, 41.5% of patients had died. The most common cause of death was from CV causes, accounting for 44% of total deaths. Thereafter, the most common reason for death was the withdrawal of RRT in the face of intractable co-morbidity, a proportion of which was also due to CVD.

It should be noted that the majority of these studies were carried out in patients using haemodialysis as mode of RRT. Large studies solely in patients on peritoneal dialysis (PD) are lacking and comparison between modalities is difficult as selection bias exists with regard to choice of mode of RRT and patients with a prior history of CVD are more likely to be placed on haemodialysis programmes. However, data from the USRDS suggests the rate of de novo IHD and CHF and mortality of patients once established on PD is similar to that of patients on haemodialysis with an annual CV mortality of 9.6% (14) and a recent review of 9 studies examining the outcome of patients on PD compared

to those on haemodialysis found no real difference after adjustment for factors such as age, diabetes and co-morbidity (32).

Around one third of patients with ESRF will be identified as suitable candidates for renal transplantation. Several studies have shown that patients identified as transplant candidates are younger, more likely to be male and have non-diabetic renal failure (1,3) than those on RRT not placed on waiting lists. Patients on transplant waiting lists are also less likely to have vascular disease and less likely to have a history of either angina or previous AMI (1,3). In the study of Oniscu *et al.* (3) patients remaining on RRT had a prevalence of IHD of 30.8% and 19.2% were diabetic. However, patients who were wait listed had a prevalence of IHD of 13.8% and only 11.2% were diabetic. Mortality is therefore around 50% that of patients remaining on RRT not felt suitable for transplant but CV mortality remains responsible for 50% deaths whilst waiting for renal transplant and the annual mortality rate of listed patients is 6.3%, which rises to 10% if the wait listed patient is diabetic (1). Recently in the UK, Sharma *et al.* (33) followed 125 renal transplant candidates for 18 months. Overall mortality during follow-up was 9.6% and 58% of deaths were due to CV causes. On average, patients wait for a renal transplant for 2 years after being listed although, with an increasing shortage of donor organs, that time is expected to rise over the next 10 years. With an average list waiting time of 5 years not unreasonable in the future, the estimated risk of a diabetic patient dying whilst awaiting transplant is 30% (34).

Peri-operatively and in the immediate post-op period, mortality actually increases to 2.5 times that of patients remaining on the waiting list (1,3,35). The majority of this excess risk is due to the CV complications of AMI, arrhythmia and cardiac arrest. In a study by

Humar *et al.* (35) the overall incidence of peri-operative cardiac complications was 6.1% in a cohort of 2694 transplant candidates and in a retrospective study of AMI in 53,300 patients awaiting transplant, Kasiske *et al.* (36) found that although the relative risk (RR) of AMI 30 days post transplant rose 2.5 times above those remaining on the waiting list (2.8% per year), with a longer period of follow up, those who were transplanted had a 17% lower risk of sustaining an AMI.

Over the first 12 months post transplant morbidity and mortality gradually decreases to below that of patients remaining on the waiting list (Graph 1.2) and after 3 years of follow up the mortality rate of patients with a functioning renal allograft is 68% less than that of remaining on the list. CV risk remains lower whilst the patient has a functioning allograft but CV mortality remains the most common cause of death, responsible for 32% of deaths in this population. On average, the life expectancy of an allograft is around 10 years and if the allograft fails and the patient requires RRT once more, CV risk again increases to 20 times that of the general population and the patients will require reassessment for renal transplantation if felt appropriate.

1.3 Cardiovascular Risk Factors and Chronic Renal Failure

For the purposes of description, the risk factors for CVD in patients with renal failure are usually split into 'traditional' and 'non-traditional'. Traditional risk factors are those that have been defined and validated in the general population through prospective cohort studies such as the Framingham cohort, namely hypertension, diabetes, hyperlipidaemia, smoking, family history of premature IHD, age and male sex (Table 1.1) (37). Patients

with CRF have a higher prevalence of many of these risk factors especially those felt, in part, modifiable; hypertension, hyperlipidaemia and diabetes.

The prevalence of hypertension is high in patients with CRF and in those who are not yet dialysis dependant is 70-80% (38-39). The prevalence of hypertension increases as GFR declines (40) and level of systolic blood pressure (BP) is directly correlated with the level of GFR and proteinuria (41). Observational studies of patients with CRF Stages 1-4 (GFR >15ml/min) have shown that hypertension is an independent risk factor for the development of LVH (42) and for CV events (18,43). Indeed, in a recent retrospective study of 184 non-diabetic patients with CRF Stage 1-4, uncontrolled hypertension (>140/90mmHg) was the strongest independent risk factor for CV mortality (RR 2.93, $p<0.001$, 95% CI=1.69-5.12) (44).

Hypertension is the norm once patients reach ESRF and over 80-90% have hypertension at instigation of dialysis (45-46). The relationship of BP and CVD in patients on dialysis is complex. Higher BP has been shown to be a risk factor for LVH, IHD and CHF (47) but a low BP has been associated with a higher risk of all cause mortality (48-49). It is generally believed that the increased risk for all cause mortality in individuals with low BP is due to underlying co-morbidity that is associated with lower BP. For example, patients with low BP may already have structural cardiac disease and therefore may be at higher risk for CVD events (17). This U shaped relationship of BP with outcome and the high prevalence of BP in this population have meant BP does not have the same strength of association with outcome in patients on RRT and few observational studies have associated hypertension with shorter survival (50) and excellent BP control with increased survival (51).

The aetiology of hypertension is also different in patients with ESRF compared to those in the general population. Increased peripheral resistance due to arteriosclerosis results in a decrease in compliance of the arterial tree and a combination of systolic and diastolic hypertension. However, volume overload secondary to salt and water retention plays a major role in the hypertension associated with ESRF and increased cardiac output (CO) secondary to arteriovenous fistulae and anaemia may also be factors (52). Thus, the treatment of hypertension in patients with ESRF may involve manipulation of dialysis programmes as well antihypertensive drug therapy (52).

Similar to the relationship of BP with outcome in patients on RRT, the relationship between dyslipidaemia and outcome also displays the phenomenon of 'reverse epidemiology' in patients with ESRF. Dyslipidaemia is common in patients with renal failure and the pattern and severity varies with the stage of renal disease (Table 1.2) (53) but hyperlipidaemia has not consistently been associated with CV outcome in patients with CRF, although it is associated with CV outcome in patients after renal transplantation (54-55). Cross-sectional studies of patients on RRT have failed to show an association between high total cholesterol and CV events (56-57), whilst other studies have shown high LDL cholesterol to be associated with CV events in patients on haemodialysis (58) and others have demonstrated a 'J' or 'U' relationship between serum cholesterol and outcome (59-60) with low and high levels of total cholesterol associated with poor outcome. With regard to the association of low cholesterol with adverse CV outcome, it is known that chronic inflammation will decrease levels of cholesterol and that inflammation is associated with an increased risk of both all-cause (61) and CV mortality (62) in patients with CRF. The prevalence of dyslipidaemia is higher in patients

with CRF than the general population and the situation is made more complex as patients established on haemodialysis have a different lipid profile compared to those on PD (Table 1.2). Thus, as with hypertension, hyperlipidaemia does not have a strong association with outcome in patients with ESRF.

In the general population, it is well recognised that diabetes is a risk factor for the development of CVD. Around 40% of patients with diabetes have reduced GFR (38) and the majority of these have diabetic kidney disease. The presence of diabetes is associated with CVD in patients with Stage 1-4 CRF (38) and increasing levels of proteinuria in diabetic kidney disease are associated with a higher risk of CVD and all cause mortality (63).

Diabetes is the cause of ESRF in approximately 40% of dialysis patients (14) and is an independent risk factor for IHD and all-cause mortality for both patients using haemodialysis (29,56) and PD (29) as mode of RRT. In the study of Foley *et al.* (64), 116 diabetic patients commencing RRT were followed up for 41 months. Compared to 315 non-diabetic patients, those with diabetes had a higher prevalence of IHD and CHF and a higher incidence of new onset IHD during the study. Both all-cause and CV mortality in the diabetic cohort were significantly higher (Graph 1.3) and the presence of either IHD or CHF at initiation of dialysis were strong predictors of death (Hazard Ratio 2.3(1.5-4.0) and 2.1(1.0-4.4) respectively). However, there are no studies examining the impact of tight glycaemic control on CV outcome in patients with CRF, although it is recognised that improved glycaemic control may reduce the progression of renal failure in the earlier stages of CRF.

Finally, with regard to potentially modifiable traditional risk factors, smoking is associated with CVD and all cause mortality at all stages of CRF, including those who have a functioning renal allograft (18,55-57). However, there are no studies that have demonstrated that smoking cessation improves CV outcome in CRF but it would seem advisable in view of the association with adverse outcome that patients are counselled regarding smoking cessation and offered the same help as those in the general population to stop smoking.

Given that the relationship of the potentially reversible risk factors of hypertension and dyslipidaemia with outcome in ESRF is inconsistent and that risk scores using 'standard' CV risk factors dramatically underestimate CV events in this population, it is widely accepted that other 'uraemic' or non-traditional risk factors exist in patients with renal failure (Table 1.1).

Atherosclerosis is increasingly recognised as a chronic inflammatory disease of the vessel wall (65) and progression of atherosclerotic plaques has been shown to be associated with secretion of pro-inflammatory cytokines and mediators, and progressive accumulation of inflammatory cells (65). Patients with renal failure, especially if on haemodialysis, have been shown to have high levels of circulating pro-inflammatory cytokines, such as interleukin-6 (66) and TNF alpha (67), and this suggests uraemia per se may cause a pro-inflammatory status with ongoing acute phase response This hypothesis is supported by finding of higher circulating levels of C-reactive protein (CRP) in patients with ESRF compared to those without renal failure (68). However, whether or not this process is modifiable with agents such as statins or aspirin is unknown.

Other uraemia related cardiac risk factors such as hyperhomocysteinemia, oxidative stress and abnormal calcium/phosphate metabolism have been identified and studied but similar to inflammation it is unknown whether modification of these factors would confer improvement in CV outcome or if these factors are even modifiable.

In the search for modifiable CV risk factors in patients with ESRF, seminal work by Parfrey *et al.* (69-71) in the mid-1990's established abnormalities of LV structure and function, namely LVH, LVDil and LVSD as independent risk factors for CV outcome in patients with dialysis dependent renal failure. Indeed, these LV abnormalities have been found to be the strongest independent predictors of outcome in this population (17). LV abnormalities are also strongly associated with adverse outcome in the general population but the prevalence, incidence and natural history of these LV abnormalities are different in patients with ESRF and due to these differences they are collectively termed 'uraemic cardiomyopathy'

1.4 Left Ventricular abnormalities and Chronic Renal Failure

Abnormalities of LV structure and function, defined by echocardiography, are more strongly associated with outcome than standard CV risk factors in patients with ESRF and have been described as being prevalent for over two decades (17,69,71-74). These abnormalities, especially LVH, are found early in the course of CRF and worsen as GFR declines (42). It is estimated that the prevalence of LVH in patients with a GFR >50ml/min is 27%, whereas in those with a GFR of 25-50ml/min the proportion is 31% which increases to 40% in patients with a GFR of <25ml/min (42).

Once patients require dialysis as many as 85% of patients have an abnormal LV as defined by echocardiography and in one of the largest of these studies, Foley *et al.* (69) reported the prevalence of LV abnormalities in a cohort of 433 patients entering a long term dialysis programme in Canada from 1982-1991. They found that 74% of the cohort had LVH, 35% had LVDil and 15% had LVSD. Only 16% of the cohort had a normal LV (Figure 1.1). Other studies have reported similar findings for the prevalence of LV abnormalities in patients who are dialysis dependant and up to 80% have been found to have LVH identified by echocardiography (75-76). The prevalence of LVH in the normal population and in patients with hypertension is much lower than that observed in dialysis patients. Data from the Framingham study suggests that the prevalence of LVH in women is up to 33% in older age groups and 23% in older men (77) whereas studies of hypertensive patients observed a prevalence of 42.2% for LVH (78).

The observed pattern of LV abnormalities in ESRF has led to the classification of three types of cardiomyopathy in this population; concentric LVH, eccentric LVH and LVSD (69). Previous groups have proposed two models for the development of the LV abnormalities in patients with ESRF (79-80). The first is caused by predominantly pressure overload with an increase in pulse pressure. Initially, this is adaptive and in theory potentially reversible but when sustained overload occurs especially if associated with non-haemodynamic factors such as inflammation or ischaemia, fibrosis can develop eventually culminating in diastolic dysfunction and heart failure. Pressure overload is associated with hypertension secondary to increased arterial calcification and arteriosclerosis with a resultant decrease in aortic compliance and distensibility and

increased aortic stiffness (80-81). This produces initially concentric LVH, an increase in relative LV wall thickness with normal LV volumes.

The second proposed model is caused by hypertension due to volume overload and produces eccentric LVH with initial dilation of the ventricle followed by compensatory hypertrophy. Renal failure, with salt and water retention, causes volume overload which is further exacerbated by the creation of arteriovenous fistulae which can increase CO by up to 25% (82-84). Anaemia also increases CO and contributes to volume overload (85). In any individual patient with ESRF both mechanisms may play a role in the development of LV abnormalities. The end-point of both mechanisms is cardiac failure and systolic dysfunction. In the case of pressure overload and concentric hypertrophy, after a period of diastolic dysfunction, eventually LV dilation will occur followed by systolic dysfunction.

Patients on dialysis who are considered candidates for renal transplantation are generally younger and fitter than those who remain on dialysis and as they have less co-morbidity it could be presumed that the prevalence of LV abnormalities is lower in this group. Studies in our own population of transplant candidates however do not support this hypothesis. In a study by McGregor *et al.* (86), 141 non-diabetic patients on the transplant waiting list underwent echocardiography just prior to undergoing renal transplant. The prevalence of LVH was found to be 70% for men and 65% for women, 83% were identified as having LVDil and 28% had systolic dysfunction, defined by Fractional Shortening (FS) <25%. However, due to the nature of the study, patients were not necessarily examined on a post dialysis day which may have overestimated the proportion of patients with LV abnormalities. In a more recent study by Sharma *et al.* (87), 203 patients on the renal

transplant waiting list in London were studied and 21% of these patients were diabetic. The prevalence of concentric LVH was found to be 60% in the whole cohort and the prevalence of eccentric LVH and LVSD was 11% and 7% respectively. Thus, whilst the prevalence of LVH remains high in those awaiting transplant, the prevalence of LVDil and LVSD may be lower than those remaining on dialysis and it is notable that in the institution where the study of Sharma *et al.* was carried out, patients with an Ejection Fraction (EF) of <30% are excluded from the renal transplant waiting list. However, in both these studies, the proportion of patients with a normal ventricle was still small at 13% and 22% respectively.

Prognosis is adversely affected by the presence of LV abnormalities (29,75-76,87) and outcome worsens progressively with the echocardiographic findings of LVH, LVDil and LVSD. With follow up of the cohort of Foley *et al.* (70) it was found that median time to the development of clinical cardiac failure was 19 months for patients with LVSD, 38 months in LVDil and 38 months in those with LVH. The rate of mortality is also higher in patients with LVSD. Median survival was found to be only 38 months if a patient was found to have LVSD whereas it was 48 months in those with LVH, 56 months in those with LVDil without systolic dysfunction and over 66 months in patients with normal ventricles (70). Around two thirds of patients on dialysis with LVH die from heart failure or sudden death and the 5 year mortality increases from 23% to 52% when comparing a LV mass index (LVMI) of less than or more than $125g/m^2$ (72).

In addition to identifying patients with a poorer prognosis, the presence of an abnormal ventricle serves as a marker or risk factor for the development of de novo CHF and IHD. For example, the presence of LVSD on echocardiography is the strongest independent

risk factor for the development of CHF in this population (RR 2.05) (30) and the presence of any LV abnormality will independently increase the risk of developing IHD with a RR of 5.92, 5.35 and 12.2 for LVH, LVDil and LVSD respectively (71).

With follow up, observational studies have shown a gradual progression of the degree of LVH and LVDil observed in an individual patient (70), although regression of LVH may be possible with manipulation of dialysis programmes (89) and tight control of BP with agents such as angiotensin converting enzyme inhibitors (ACEI) (75). Regression of LVH and LVDil is also observed after renal transplantation (90-91) and pre-transplant LV abnormalities have been shown to be predictive of CV outcome after renal transplantation (86-87). Recently, the work of Zocalli *et al.* (76,92-93) has shown that the strongest prognostic indicators of outcome in patients with ESRF are the LV abnormalities of LVH and LVSD, especially if the degree of magnitude of these abnormalities worsens with time and in a study by Paoletti *et al.* (94) worsening LVH in patients with ESRF was the strongest predictor of sudden death after 10 years of follow up. These findings suggest that serial monitoring of LV abnormalities may provide additional prognostic information over a single measurement.

Several studies have examined potential risk factors for the development of LV abnormalities and have found that risk factors differ depending on type of LV abnormality found on echocardiography. Systolic hypertension has most consistently been associated with the development of concentric LVH (29,42,69,74) and anaemia has also become inseparably linked with LVH in nephrology literature. Factors associated with progression of LVH include age and diabetes (69,71). Anaemia has been more strongly associated with eccentric LVH than with concentric LVH (75) and other factors

such as hypoalbuminaemia and haemodialysis as mode of dialysis therapy have also been found to accelerate progression of LVDil and a history of IHD may also play a role. LVSD implies a poor outcome in this patient population and is associated more consistently with a history of IHD and diabetes. Again, other factors such as BP and anaemia have been associated with LVSD but with much less consistency than that of IHD (71,92,95).

Despite a wealth of data on the epidemiology of echocardiographically defined LV abnormalities in ESRF and the association of potentially reversible risk factors such as hypertension and anaemia with these abnormalities, there is still a lack of interventional trials to show that targeting reversible risk factors produces regression of LV abnormalities thereby translating into improved outcomes. One recent study by London *et al.* (75) targeting both hypertension (pre-dialysis BP>140/90mmHg) and anaemia (Hb<11.0g/dL) in 153 dialysis patients, produced regression of LV mass of 10% in 46% patients in the study and 'responders' had improved outcome compared to non-responders. This study of London *et al.* is the first to suggest CV outcome can be improved via regression of LVH in dialysis patients but as yet there is still no major evidence base to support the hypothesis that aggressive risk factor targeting and regression of LV abnormalities will impact upon either CV or all cause mortality in this population.

Part of the problem with using LV abnormalities as targets in interventional studies in patients with ESRF is the inaccuracy of echocardiography as the method of measurement in this population. However, several other problems also exist. Firstly, LV abnormalities of structure and function are interrelated and often coexist together giving a 'chicken and

egg' scenario once established. Secondly, LV abnormalities are also a risk factor for CV outcome and a disease state themselves, further complicating the issue and finally, the relationship of LV abnormalities to CAD is not clearly defined in this population due to the difficulties of non-invasive characterization of CAD and a high prevalence of symptoms such as chest pain and breathlessness, which although suggestive of underlying CAD, may be due to other conditions such as volume overload and anaemia. Anaemia has been consistently listed as a risk factor for both CVD and cardiomyopathy in patients on RRT and the majority of interventional trials targeting LV abnormalities have been via treatment of anaemia in this population. However, there are no trials showing that reversal of anaemia alone improves CV outcome or produces regression of LVH in patients with renal failure and the association of haemoglobin with LVH in this population may be because of inaccuracies in the current methods used for calculation of LV mass.

1.5 Haemoglobin and Left Ventricular abnormalities

There are several explanations for the anaemia found in association with CRF, including inhibition of marrow erythropoiesis by humoral toxins, bleeding, shortened life span of erythrocytes and malnutrition, but the primary cause is a decline of erythropoietin production by the failing kidney (96). The anaemia associated with renal failure is typically normochromic and normocytic and the severity increases with decreasing GFR. Anaemia develops when GFR falls to between 25-50ml/min (97) and, with the discovery of erythropoietin and eventual manufacture of recombinant human erythropoietin,

treatment of anaemia in patients with CRF changed dramatically, with the need for recurrent blood transfusion significantly reduced (96).

However, a significant proportion of patients with CRF, especially those with ESRF, remain anaemic and current guidelines suggest a target haemoglobin concentration of more than 11g/dL in such patients (98). At tissue level, anaemia leads to hypoxia, vasodilatation and increased venous return (99). This in turn affects measured end-diastolic volume (EDV) and anaemia has been associated with LVDil in several previous echocardiographic studies (42,71,74,100). It is postulated that initial LVDil caused by anaemia in CRF will lead to eccentric LVH and thus anaemia is also associated with LVH in ESRF. Anaemia in CRF is associated with increased morbidity and mortality (101-102). Large retrospective studies of patients on haemodialysis programmes have suggested an increase in mortality rate as haemoglobin declines and that patients with haemoglobin concentrations of <8g/dL have twice the rate of mortality of those with concentrations of between 10-11g/dL (101). Treatment of anaemia with erythropoietin is associated with outcomes such as improvements in quality of life (103), exercise tolerance (104), immunity (105) and sexual function (106) and decreases frequency of hospitalization (12). However, the degree of anaemia correction conferring optimal mortality benefit is less certain and anaemia correction has not directly been shown to confer mortality benefit in either CRF or ESRF (107-108).

In a recent study published by Singh *et al.* (107), 1432 patients with CRF were randomised to receive erythropoietin targeted to achieve either a haemoglobin concentration of 13.5g/dL or 11.3g/dL and had a composite end-point of death, myocardial infarction or hospitalisation for CHF and stroke. They found no benefit to

targeting haemoglobin concentration to the higher level and the number of adverse events was actually higher in the group whose target haemoglobin concentration was 13.5g/dL. Another study by Drueke *et al.* (108) targeted those with a GFR of between 15-35ml/min and mild anaemia (11.0-12.5g/dL) to either a target haemoglobin concentration of 13.0-15.0g/dL or 10.5-11.5g/dL. The primary end-point was a composite of 8 CV end-points with a secondary end-point of LVH regression. Again, at the end of this 3 year study no improvement in CV outcome was found and no differences in LV mass between groups. In both studies quality of life and general function improved. Other studies such as the Normalisation of Haematocrit Trial (109) included patients on haemodialysis with the presence of IHD or CHF. Patients were targeted to a higher (42%) or lower haematocrit (30%) level and again no benefit was found with regard to mortality or CV events and the trial was stopped early due to an excess of vascular access thrombosis in those targeted to a higher haematocrit level.

The association of anaemia directly with LV abnormalities such as LVH has come mainly from observational trials (42,71,100) and several of these have found anaemia to be a risk factor for LVDil and LVH as well as new onset CHF. Thus the hypothesis in many subsequent articles involving anaemia and patients with ESRF (110-112) has been as follows; LVH defined by echocardiography is common in patients with ESRF and is associated with increased CV mortality; anaemia is a risk factor for LVH and de novo CHF; regression of LVH in patients with hypertension results in a reduction in CV events in patients without renal failure; anaemia correction will lead to regression of LVH and therefore, CV outcome will be improved in patients with ESRF by anaemia correction. This hypothesis supposes that LVH and LV dilation are mechanisms via which anaemia

affects mortality and that LVH is an attractive surrogate end-point for CV outcome in trials of anaemia correction. This strategy is questionable due to the lack of interventional studies demonstrating that anaemia correction improves clinical events in parallel with a predictable change in LV geometry or function.

There have been several small, uncontrolled interventional trials targeting anaemia which suggested variable reduction of LV mass or LV dilation (113-115). However, in a larger double blind randomised controlled trial, Parfrey *et al.*(116) randomised haemodialysis patients with echocardiographically defined cardiomyopathy to a targeted haemoglobin concentration of either 9.5-10.5g/dL or 11-13g/dL. No regression of concentric LVH or LVDil was found resulting from normalisation of haemoglobin, although it was suggested that reversal of anaemia may prevent new LVDil. It was commented upon by the authors that patients on haemodialysis with evidence of cardiomyopathy may be at a too advanced stage to benefit from anaemia correction.

There is little data supporting the relationship of correction of anaemia and LVH in patients with CRF either. Two studies totalling 20 patients reported LVH regression in association with erythropoietin treatment but as these studies were uncontrolled, the effect of other parallel processes cannot be dismissed (117-118). In a larger randomised trial involving 153 patients with a GFR of between 15-20ml/min, patients were assigned to target haemoglobin concentrations of either 9.0-10.0g/dL or 11.0-12.0g/dL (119). Follow up was over 2 years and the primary end-point was a change in LV mass index (LVMI), measured using echocardiography. No significant differences were found between the 2 treatment arms at the end of the study with regard to LV mass or volumes and a small increase in LVMI in those found to have no LVH at the commencement of

the study showed no relationship to haemoglobin. Similar findings were observed in a recent study by MacDougall *et al.* (120) who studied 197 patients with a serum creatinine of <500mmol/L. Patients were treated early when they first developed anaemia (Hb <11.0g/dL) and compared to a group who were not treated until haemoglobin fell below 9.5g/dL. Again, there was no significant difference found with regard to the primary end-point of LV mass between the two groups after three years follow up.

However, the use of LVH in patients as a surrogate end point of CV outcome in this population still remains an attractive one in light of the results of the previously mentioned interventional trial by London *et al.* (75). This study assessed the impact of targeting both anaemia and BP on LVH. This strategy produced partial but significant regression of LVH which conferred a mortality benefit. However, it is unclear how much BP reduction influenced the results and perceivable, in light of other evidence, that BP reduction resulted in all of the positive findings. It is important to ascertain how much of an impact each of these reversible risk factors has on end-points such as LVH, as treatment of anaemia with erythropoietin can elevate BP. The findings of London *et al.* also do not support the argument of Parfrey *et al.* that regression of LV abnormalities in patients on haemodialysis may not be possible due to the advanced stage of cardiomyopathy.

Despite the consistent association of anaemia with LVH, there is no reliable evidence that reversal of anaemia either improves LV abnormalities or patient outcome. It is likely that this 'mismatch' in evidence base is partly due to the inaccuracies associated with echocardiographic measurements of LV mass and volumes and the relationship between

anaemia and LV abnormalities may be better understood using more accurate measurement techniques.

1.6 Brain Natriuretic Peptide and Left Ventricular abnormalities in ESRF

The natriuretic peptides are a family of peptides, discovered in 1981, with a potent natriuretic, diuretic and vasorelaxant activity, the physiological effects of which are shown schematically in Figure 1.2 (121). The family consist of three peptides; atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP). ANP, produced primarily in the cardiac atria and BNP, produced mainly in the cardiac ventricles, are released in response to increased myocyte stretch with an increase in atrial and ventricular wall tension respectively, both reflecting increased intravascular volume (121).

Both ANP and BNP are initially produced in a pre-cursor protein form and are cleaved to the active form and inactive NT-proANP and NT-proBNP. Both the active and inactive forms of ANP and BNP circulate in the plasma and can be measured. ANP and BNP as well as NT-proANP and NT-proBNP have been shown to have elevated levels in patients with LVSD (122-123), LVH (124-125) and CAD (126) and are strong predictors of CV morbidity and mortality in such patients (126-127). Furthermore these peptides, particularly BNP and NT-proBNP can be used to help diagnose heart failure in the general population due to the very high negative predictive value (NPV) of this test (123,128) and it has been suggested that levels can be used in the tailoring of medical therapy in heart failure to improve prognosis (129).

Recently, the use of BNP and NT pro-BNP has been examined in patients with advanced heart failure awaiting cardiac transplant and in patients after transplant. Gardner *et al.* (130) studied 26 consecutive patients undergoing cardiac transplantation, measuring NT pro-BNP level at the time of listing for transplant and 1 week post transplant. They found that NT pro-BNP level was predictive of mortality post cardiac transplant and previous work by the same group suggests NT pro-BNP is also a strong independent predictor of mortality in patients whilst awaiting cardiac transplant. An earlier study by Mehra *et al.* (131) measured BNP in 62 patients who had undergone cardiac transplant more than 12 months previously. Patients were followed up for 24 months and BNP as well as a low EF were found to be independent predictors of poor survival.

It therefore follows, that in view of the association of LV abnormalities with outcome in patients with ESRF and the fact that CVD is the most common cause of death both whilst patients are awaiting renal transplant and post-transplant, natriuretic peptides could form a useful adjunct in the investigation of CVD in such patients. However, the measurement of these peptides is more complex in patients with renal failure for several reasons. Firstly, fluid retention and increased intravascular volume and therefore venous return, will cause stretch of the atria and ventricles increasing the production of ANP and BNP. Secondly, the kidney is in part responsible for excretion of these peptides and both ANP and BNP circulate in higher levels in the plasma in patients with CRF than in patients with normal renal function and levels progressively increase with a decrease in GFR (132-136). Thirdly, in patients on haemodialysis levels of ANP and BNP change depending on the time the sample is taken with regard to dialysis cycle (134,137) and depending on whether high or low flux dialysis membranes are used (137) and finally

levels are further elevated in patients with ESRF who have LVSD, LVH or CAD (129,138-139). It has also been suggested that there are also other confounding factors in patients with renal failure which influence natriuretic peptide levels including haemoglobin levels and albumin (136).

In renal failure, several studies have shown that BNP is a more sensitive and specific marker than ANP for the assessment of LV abnormalities (137,140). BNP is a 32 amino acid structure and has a molecular weight of 3472Da. Most dialysis membranes will clear mid-molecular weight molecules including BNP but high-flux membranes will give a higher rate of clearance (138). Several studies have suggested that BNP levels do not change after dialysis (141-142) but others have found that levels decrease (133,137,143). Recently Zeng *et al.* (134) performed a study in 56 patients on long term haemodialysis, measuring BNP levels pre-dialysis, immediately post dialysis and again at 3hours, 6hours and 24hours post dialysis. They found that levels of BNP were elevated from pre-dialysis level immediately post-dialysis and then fell below pre-dialysis level for the remaining test times. In another study, Nishikimi *et al.* (138) found that levels of BNP fell after dialysis except on a Monday, after the patients had an extra 24 hours without dialysis compared to other times of the week. However, despite these differences in levels of natriuretic peptides at differing times between dialysis sessions Zeng *et al.* found that the timing of sampling did not significantly change the sensitivity and specificity of BNP to predict LV abnormalities.

Recently, it has been suggested that in patients with normal renal function NT-proBNP is more sensitive and specific than BNP for identifying LV systolic and diastolic dysfunction and a more powerful predictor of outcome (144). NT-proBNP is a much

larger molecule than BNP with a molecular weight of 85 Da, and also has differing methods of excretion. In addition to glomerular filtration, BNP is eliminated from plasma mainly through natriuretic peptide receptors NPR-C, and degraded by neutral endopeptidases (145-146). In contrast, NT pro-BNP is largely eliminated by glomerular filtration only (147). In our own population, we performed a pilot study to assess the potential use of NT-proBNP as a marker of LV abnormalities in dialysis dependant renal failure. We studied 25 patients on haemodialysis and measured levels of NT-proBNP immediately before, halfway through and immediately after haemodialysis. The normal level of NT-proBNP is <90picomoles/L and we found grossly elevated levels of NT-proBNP at all three time stages. Mean NT-proBNP level was 88,164 picomoles/L, the range of NT-proBNP was very large and levels further increased after dialysis. This finding has been shown in other studies of NT-pro BNP in patients on dialysis (147) and NT pro-BNP is eliminated by high flux dialysis membranes but not by low flux dialysis membranes. In view of the added potential problems with NT pro-BNP and a seemingly superior sensitivity and specificity of BNP compared to ANP in detecting LV abnormalities in patients on haemodialysis we elected to measure BNP in our cohort of patients.

However, not all patients awaiting renal transplantation use haemodialysis as mode of RRT and a significant proportion use continuous ambulatory PD (CAPD) or ambulatory PD (APD). There is little data on levels of natriuretic peptides in patients on CAPD or APD but one small study comparing 32 patients on CAPD to 63 patients on haemodialysis suggested that BNP and ANP levels are significantly lower in patients on CAPD after patients with IHD had been excluded. The authors suggested that this may be

due to the lower haemodynamic load in patients on CAPD and BNP correlated with positively with LVMI and negatively with EF in both subsets of patients (148).

It is unsurprising in view of the numerous confounding factors contributing to the circulation of these peptides in patients with renal failure that their usefulness in the diagnosis of LV abnormalities in this population, as well as their potential role in monitoring disease and as a marker for prognosis is unclear. Previous studies assessing the role of these peptides in CRF have all used echocardiography as the method of measurement of LV abnormalities. CMR imaging is now the accepted standard of reference for measurement of LV mass, volumes and function (149) and the relationship between BNP and LV abnormalities in patients with ESRF may be better defined using CMR measurements of LV structure and function.

1.7 Left Ventricular abnormalities and Coronary Artery Disease

The mode of cardiac death in patients with ESRF is different to that of the normal population. Whereas the majority of deaths in the normal population are due to obstructive CAD, only around 20% of cardiac deaths are due to the direct consequences of AMI in patients with ESRF (150). The majority of the mortality in this population is due to sudden, presumed arrhythmic death (150) explained partially by large electrolyte shifts associated with dialysis, abnormal physiological loading conditions (151) and reduced subendocardial capillary density with resultant relative hypoperfusion secondary to LVH (79). However, it is also likely that a proportion of arrhythmic death in this population is due to underlying 'silent' CAD.

There are other differences between CAD found in the normal population and that in patients with renal failure. The composition of coronary plaque may be different in patients with ESRF, with increased media thickness and more marked calcification of the affected coronary arteries compared to those of the normal population, in whom plaque morphology tends to be fibroatheromatous (152-153). An increase in media thickness is not confined to the coronary conduit arteries in patients with CRF but is widespread from small resistance arteries to the aorta (80-81,154), in part, resulting in an increase in vascular stiffness and non-compliance.

Angiographic studies of patients with ESRF suggest that up to 50% have significant and often silent CAD and defining those patients with CAD is important as it affects treatment and prognosis (155-157). AMI is an early hazard in patients starting dialysis with 29% sustaining an AMI within the first year of dialysis and 52% within two years of initiation of dialysis (158) and in this population AMI is an event that is associated with a very poor long term survival (158-160). Several studies have shown that mortality rate at 12 months post AMI in this population is as high as 60% and two year mortality up to 73% (158). Patients have a better outcome after renal transplantation but mortality is still significantly higher than that of the normal population with a two year mortality rate of 34% (159) and around 45% of deaths in the first 12 months after renal transplant are due to AMI (1,161). The very poor outcome in patients on dialysis is felt to be, in part, due to a combination of under diagnosis, as many patients may present atypically with symptoms that could also be attributable to fluid overload, and under treatment or 'therapeutic nihilism' (162-163). Patients established on RRT are less likely to receive thrombolysis (164) in the event of an AMI even though outcome is even more dismal if

thrombolysis is not administered in this population (165) and patients with ESRF are also less likely to undergo percutaneous intervention (PCI), receive glycoprotein IIb/IIIa receptor antagonists or be discharged on optimal secondary prevention with beta-blockers or statins (163,166-167). Again, this is despite the fact there is evidence to suggest that administration of glycoprotein IIb/IIIa inhibitors provide similar benefits in patients with renal failure (168-169), at the cost of a moderately increased risk of non-fatal haemorrhage, and that patients with ESRF have a better long term outcome after AMI if prescribed aspirin, beta-blockers and ACEI's (166,170).

LV abnormalities, defined by echocardiography, are generally considered and investigated separately to CAD in patients with renal failure in nephrology literature and there are few studies comparing the findings of coronary angiography to those of resting echocardiography and LV abnormalities. Longitudinal studies investigating LV abnormalities tend to use a history of angina or previous AMI as a marker of CAD (17,29), as repeated coronary angiography would be impractical and unethical, and the few studies using coronary angiography to investigate CAD in this population that also involve resting echocardiography, have incomplete echocardiographic data as echocardiography was carried out at the discretion of the referring physician (171).

Several studies investigating the risk factors for the development of de novo IHD suggest an echocardiographic finding of LVSD was the strongest predictor of developing symptoms of IHD (29). A finding of LVH or LV dilation (LVDil) was also associated with an increased risk of developing IHD (29) but as previously mentioned, IHD was defined clinically and it is well recognised that patients with renal failure and LVH may

develop typical symptoms of angina with normal coronary arteries due to relative hypoperfusion of the subendocardial layer of the myocardium.

The non-invasive identification of LV abnormalities is relatively straightforward in this population compared to the non-invasive identification of CAD. The ability of non-invasive stress imaging modalities to both identify reversible myocardial ischaemia and predict prognosis in this population has been generally disappointing. Exercise tolerance testing (ETT) in patients with ESRF is unsatisfactory as patients have poor exercise tolerance secondary to factors such as anaemia, PVD and general deconditioning and there is a high prevalence of abnormalities found on the resting electrocardiogram (ECG) making interpretation difficult (33,172). The accuracy of single-photon emission computed tomography (SPECT) nuclear stress perfusion imaging in renal transplant candidates, compared to quantitative coronary angiography (QCA), is better than that of conventional ETT but still does not reliably provide a sensitivity or specificity of over 80% (173-174) and there are no studies using positron emission tomography (PET) scanning in this population, which is widely regarded as the standard of reference for the non-invasive detection of CAD in the normal population. There are relatively few studies using dobutamine stress echocardiography (DSE) in patients with ESRF with mixed results. In a study of 50 renal transplant candidates, Herzog *et al.* (175) found a sensitivity of 75% and specificity of 76% for DSE to detect a >70% coronary stenosis defined using QCA and more recently, Sharma *et al.* (33) found the sensitivity of DSE to detect a coronary stenosis of >70% to be 88% with a specificity of 94% in a cohort of 125 renal transplant candidates. However, other groups have not found DSE to be predictive of coronary anatomy or future cardiac events in renal transplant candidates and many

found difficulty in interpreting the wall motion of the LV due to LVH and suboptimal achievement of adequate stress due to the need for early termination of the test by a markedly hypertensive response to dobutamine (171). Although observational studies have suggested there is no predictive value of non-invasive testing in patients awaiting renal transplantation (13), a meta analysis of 8 nuclear and 4 stress echo studies did show that a the finding of a positive test increased the relative risk of both future AMI and of cardiac death (176).

Several groups have argued that patients with ESRF should undergo coronary angiography to define CAD if being considered for renal transplant (155,171). This strategy is also problematic. Firstly, this is an invasive procedure with a risk of cerebrovascular event, AMI and death. The majority of patients with ESRF will have this procedure performed via the femoral approach due to the presence or potential need of arterio-venous fistulae and with the femoral approach there is a potential higher risk of dissection, pseudo-aneurysm or significant haemorrhage than that of the normal population due to the vasculopathy of renal failure. Secondly, contrast nephropathy is a real risk to patients not yet established on RRT or those with residual renal function on PD. Thirdly, if significant CAD is found, then what is the correct treatment strategy? Many of these patients are asymptomatic and the benefit of revascularization in asymptomatic patients is unknown. Recent evidence in a study of 2287 patients with CAD randomised to either medical therapy or medical therapy plus PCI showed no additional morbidity or mortality benefit of PCI over medical therapy after almost 5 years of follow-up (177). There is scant data comparing optimal medical management to PCI in patients with ESRF for the treatment of CAD and patients with ESRF undergoing PCI

have twice the restenosis rate of the general population and almost ten times the mortality (178). Data comparing PCI to coronary artery bypass grafting (CABG) in this population favours CABG (179-180). Finally, there are potential flaws in the use of QCA in the assessment of significant, physiological 'flow limiting' stenoses of the coronary arteries. A recent meta-analysis of 31 studies comparing QCA to measurements made using fractional flow reserve (FFR), which is now considered the standard of reference for physiological significance of a coronary stenosis, suggests that QCA does not predict the functional significance of CAD and that non-invasive methods of measurement such as DSE and PET actually compare better with FFR than QCA (181). As yet, there are no studies using FFR in this population and future studies utilizing coronary angiography should be wary of using QCA as the standard of reference for the functional significance of a coronary stenosis. However, the presence of CAD at angiography using QCA does give information regarding prognosis in patients awaiting renal transplant (171).

A more accurate non-invasive, combined assessment of both LV abnormalities and of underlying CAD would therefore be attractive for the CV investigation of patients with renal failure both to better define the relationship between LV abnormalities and CAD and to potentially negate the need for invasive coronary angiography, especially in asymptomatic patients.

1.8 Echocardiography and the Uraemic Heart

Echocardiography is a widely available, inexpensive and easily performed method of assessment of cardiac structure and function allowing direct visualisation of the myocardium and real time imaging (Figure 1.3). It has been utilised extensively in

longitudinal and cross sectional studies of LV abnormalities in patients with ESRF (69-76) and undoubtedly gives valuable information regarding prognosis (71-72,75-76,86-87). However, problems regarding both image acquisition and the geometric assumptions required for calculation of LV mass and volumes from one and two dimensional images of a 3-dimensional structure introduce error and affect both the accuracy and reproducibility of this method. The resulting wide range of variability raises questions regarding the utility of echocardiography to accurately detect progression or regression of LV abnormalities over time unless study sample sizes are very large (182-183).

Obtaining good quality images depends on a skilled operator, patient position and anatomy, obesity and angle of the transducer beam. Therefore, the first problem with echocardiography is obtaining images of sufficient quality for analysis which may exclude up to 25% patients (184-185). For example, in the study by Foley *et al.* (69) one of the entry criteria to the study was a satisfactory echocardiogram within 6 months of starting haemodialysis. Despite this, a further 16% of the initial cohort was excluded from the study on follow up due to inability to gain adequate images from echocardiography.

Both M-mode (one-dimensional) and two-dimensional imaging can be employed to calculate LV mass. M-mode imaging allows better endocardial border definition as it has greater resolution due to a higher frame rate, as long as adequate beam positioning is ensured and ventricular shape is normal. Two-dimensional imaging on the other hand depicts the 'real' ventricular shape and identifies regional wall motion abnormalities. However, the quality of two-dimensional imaging may be limited due to both lower lateral resolution and frame rate. Additionally, this option is more time consuming and in

all but the most recent studies in patients with ESRF, M-mode measurements have been used to calculate LV mass, volumes and function.

M-mode measurements of ventricular wall thickness and chamber dimensions and the method of cubed formulae, incorporates only one dimension of the LV cavity and assumes an ellipsoid geometry. Therefore any inaccuracy is amplified even in normal ventricles, such that a difference of 5% in the M-mode measurement will translate to a difference in LV mass of 8-15% (186).

Further problems arise due to the fact there are several formulae or measurement conventions for the calculation of LV mass and although more recently the American Society of Echocardiography (ASE) convention (187) has become the most widely used in epidemiological studies, earlier studies used any one of 3 conventions which are not interchangeable and can lead to differences in mass estimation by up to 18% (188). These conventions differ on the inclusion or exclusion of echoes from interfaces of the LV cavity or myocardial wall. These echoes are created by the fact that ultrasound signals are reinforced where surfaces change density and this allows the definition of limits between surface layers (Figure 1.4).

Initial M-mode standard convention recommended inclusion of the edges as part of the interventricular septum (IVS) but exclusion of the posterior wall epicardial edge and was calculated thus (189);

$$\text{LV mass} = 1.05\,([\text{LVIDD} + \text{PWTD} + \text{IVSTD}]^3 - [\text{LVIDD}]^3\ \text{g}$$

LVIDD= LV internal diameter in diastole, PWTD= Posterior wall thickness in diastole, IVSTD= Interventricular septum thickness in diastole

Subsequently Devereux suggested a modified regression equation derived from the post-mortem findings of 34 patients using the Penn convention as border definition where all edges are considered part of the ventricular cavity (Figure 1.4) thus (190);

LV mass = 1.04 ([LVIDD + PWTD + IVSTD]^3 - [LVIDD]^3 - 13.6g

Finally the ASE convention was proposed (187) and has become the most accepted border definition criteria using the leading edge of each layer (Figure 1.4) . Devereux *et al.* (191) then proposed a new adjusted equation using the ASE convention based on the post mortem specimens of 54 patients thus;

LV Mass = 0.8 (1.04 ([LVIDD + PWTD + IVSTD]^3 - [LVIDD]^3)) + 0.6g

Therefore, employing different conventions and formulae will result in differing calculations of mass from the same M-mode image and using the Penn as opposed to the ASE convention will result in a difference in calculated LV mass of 15% in men and 18% in women (188). This makes comparison of LVH studies using different methods of measurement difficult (192) and each can lead to different cut point values for LVH. Furthermore, the post-mortem validation studies had limited sample sizes and evaluate heterogeneous ventricular configurations and another post mortem study revealed only moderate correlation between echocardiographic and post mortem findings (193).

The problems associated with image acquisition and geometric assumptions apply to all patients undergoing echocardiography but additional problems exist when performing echocardiography in patients with renal failure. The calculation of LV mass from M-mode measurements is critically dependant on LVIDD and changes in loading conditions will temporally affect ventricular volumes and therefore also affect the measurement of LVIDD. The unique problem of the assessment of LV volumes and function in patients

with ESRF was demonstrated very simply by Nixon *et al.* (194). They studied 5 patients who were not on cardiac medication and in whom initial echocardiography demonstrated a normal ventricle and therefore the inaccuracies inherent to the geometric formulae minimised. They performed echocardiography after three different dialysis regimes were performed in each patient; haemodialysis with volume loss, ultrafiltration with volume loss only and haemodialysis without volume loss. Echocardiography was performed in each patient before and after each type of dialysis and the results analysed by two independent cardiologists who were blinded to patient name and type of dialysis. They found that even in dialysis patients with normal ventricles both EDV and end-systolic volume (ESV) altered significantly depending on type of haemodialysis therapy as did FS. In patients who had volume loss only, there were significant decreases in EDV and ESV with a decrease in EF of around 20% due to a downward shift on the Frank-Starling curve. This contrasted to the findings in the other two groups were EF increased with differing degrees of change of EDV and ESV.

Further work by Harnett *et al.* (195) found that due to the dependency of the calculation of LV mass on LVIDD, mass measurements could change by 20% in the same patient from images taken before and after a single dialysis session and thus patients with ESRF undergoing echocardiography should be studied on a post-dialysis day. However, this will not abolish the inaccuracies completely and as LV volume is calculated from M-mode measurements using the formula;

$(LVIDD)^3 \times 0.001047/Body\ Surface\ Area\ (BSA)$

and FS is calculated using the formula

[LVIDD-LVESD/LVESD] x 100, there will also be inaccuracies in the calculation of volumes and function of the LV.

It is therefore unsurprising that the reproducibility of echocardiographic measurements are variable and whilst interstudy reproducibility (test, retest variability) has a standard deviation (SD) of 22-40g (95% CI 45-78g) (183,191,196-198), interobserver variability has a standard error of estimation (SEE) of 28-41g (95% CI 55-80g) (191,197-198). This wide range of variability affects accuracy, which for M-mode imaging has a SEE of 29-97g (95% CI 57-190g) (190-191,199-200) and in a clinical setting this means that in an individual patient, M-mode echocardiography cannot detect a change unless it is more than +/-45-78g, with any certainty. It is also likely that the high variability of measurements produced by echocardiography is largely responsible for the lack of reliable evidence in patients with ESRF that LV abnormalities are reversible and that regression of these abnormalities translates into improved outcome.

These problems with echocardiography, along with the emergence of CMR imaging have led to questions being raised about the accuracy and utility of echocardiography in longitudinal and interventional studies in the hypertensive population (183,196,201) and several studies have suggested that, in the presence of an abnormal ventricle, echocardiography can both underestimate and overestimate LV mass (202-203).

Recent developments such as the use of contrast and 3-dimensional echocardiography have led to improvements in the accuracy associated with this technique but problems remain with acoustic windows and the standard of reference for the measurement of LV structure and function is now CMR imaging. Indeed, studies assessing these more recent

developments in echocardiographic technique have used CMR as the 'gold standard' comparison (204-205).

1.9 Cardiovascular Magnetic Resonance Imaging

Over the last 10 years CMR imaging has become well established in clinical practice and is now the accepted standard of reference for the measurement of left and right ventricular function, mass and volumes (206-208). Its superiority with regard to accuracy and reproducibility is due to a combination of high spatial and temporal resolution and the ability to image in any desired orthogonal plane giving 3-dimensional coverage of the heart. Initially, a fast low angle shot (FLASH) imaging sequence was used but more recently a steady-state free precession (SSFP) sequence has become the routine method for cine imaging as this provides better contrast between myocardium and blood pool, although both sequences have similar reproducibility (209).

For a CMR 3-dimensional volume and mass assessment, a set of contiguous short axis slices covering the entire ventricle from base to apex is acquired, which is planned from the horizontal long axis (HLA) view. The ventricular volume is the sum of the endocardial areas multiplied by the interslice distance, calculated at end-diastole and end-systole, and the ventricular mass is the area occupied between the endocardial and epicardial border multiplied by the interslice distance. Thus, CMR measurements of mass and function take into account any regional abnormalities of the ventricle and are independent of any geometric assumptions.

The accuracy of CMR measurements of LV mass has been validated on post mortem specimens in vivo in animal studies (210-211) and ex vivo in human studies (196,212).

These showed good agreement between CMR measured mass and the actual LV mass with a SD of difference of 8g (95% CI+/-15g) in human studies and 10g (+/-19g) in animal studies (dogs). Reproducibility of CMR measurements is also superior to that of echocardiography. Interstudy variability has a mean weighted SD of difference of 7.8g (95% CI +/-15.3g) (182,196,198,212-215) and the mean weighted intra and interobserver variability's are 4.8g and 9.0g respectively (213,216). By comparison the corresponding mean weighted interstudy SD of the difference for M-mode and two-dimensional echocardiography is 27.7g (183,196-199,201,217) and 19.2g (217-218) respectively.

The improved reproducibility of CMR means that in group studies much smaller sample sizes can be used to detect change in LV mass or, using the same sample size, smaller degrees of change can be detected. Bellenger *et al.* (213) showed that in order to detect a change of 10g in absolute LV mass with 90% power, 13 patients would be required using CMR, whereas 162 patients would be required using M-mode echocardiography, resulting in a 95% decrease in the sample size needed. It is now therefore recommended that CMR is used in studies targeting LV mass.

CMR has now become established as a Class 1 indication for the investigation of cardiac disease in several other areas (206). Due to its superior spatial resolution and three dimensional visualization, it has become the investigation of choice for cardiomyopathies such as apical hypertrophic cardiomyopathy and those affecting the anterolateral free wall which are difficult to diagnose with echocardiography, especially in the early stages of the disease and difficult to exclude by echocardiography in relatives of affected patients (219-221).

More recently, the assessment of cardiomyopathy has been revolutionised by a CMR technique called 'late gadolinium contrast enhancement' (LGCE) which allows non-invasive identification of abnormal myocardial tissue (222-223). This technique uses a gadolinium based magnetic contrast media to visualise myocardial fibrosis and necrosis and put simply, the T1 weighted images acquired after intravenous administration of gadolinium chelates show the damaged myocardium as bright areas (Figure 1.5). The mechanism of myocardial hyperenhancement is demonstrated in Figure 1.6 (224). The mechanism is based on two facts. Firstly, gadolinium chelates are extracellular and freely distribute in extracellular water but cannot cross intact cell membranes. Secondly, in normal myocardium, myocytes are densely packed and thus myocyte intracellular space forms the majority (85%) of the space. Therefore the volume of distribution of gadolinium in normal myocardium is very small and no hyperenhancement is visualised. In the setting of, for example, AMI there is myocyte membrane rupture which allows additional gadolinium to diffuse into what was previously intracellular space. This, in combination with delayed washout kinetics, results in an increased gadolinium concentration and hyperenhancement. In the setting of chronic infarction, myocytes are replaced with collagenous scar. In this situation the interstitial space is expanded which again leads to increased gadolinium concentration and hyperenhancement.

Expanded extracellular space in the myocardium can also be caused by pathological processes other than MI such as fibrosis, protein infiltration and possibly myocardial disarray with disordered myocardial fibre packing, allowing tissue characterization of non-ischaemic cardiomyopathy (NICM) as well as ICM. Studies have demonstrated that in the context of ICM, a combination of cine and LGCE CMR imaging is effective in

detecting the presence, location and extent of myocardial infarction and predicting improvement in contractile function following revascularisation in both the acute and chronic setting (225-232).

The combination of LGCE and cine CMR can also differentiate ICM from NICM with an accuracy of over 90% (225-226). Wu *et al.* (232) were the first group to report that LGCE could differentiate ICM from NICM. In their study almost all patients with ICM, diagnosed by QCA, displayed the typical hyperenhancement pattern associated with ICM whereas none of the patients with NICM had hyperenhancement. Several studies have followed including that of McCrohon *et al.* (225) of 90 patients with LVSD made up of 27 with ICM and 63 with NICM, defined on the basis of QCA. Again, all patients with ICM had typical hyperenhancement whereas only 13% of those with NICM displayed hyperenhancement. This group was made up of a proportion with mid-wall LGCE not typical of that observed with ICM and a small number that did display the typical pattern of LGCE observed with ICM. The assumption was that these patients did indeed have ICM due to previous coronary artery plaque rupture with recanalisation post event and thus no significant CAD observed at angiography. Finally Patel *et al.* (226) recently investigated 234 consecutive patients presenting with LVSD, with an EF of less than 30% and an unclear aetiology for the cardiomyopathy. Patients underwent both CMR with LGCE and coronary angiography and the authors found that the diagnosis of ICM could be diagnosed using LGCE with a sensitivity of 92% and a specificity of 93% compared to the reference standard of QCA.

In ICM, LGCE is distributed in the territory of the supplying coronary artery and always involves the subendocardium (227-228) (Figure 1.5). LGCE can differentiate

subendocardial from transmural infarction which is the basis for defining the viability of the myocardium supplied by the diseased coronary artery. With NICM, typically, there is an absence of LGCE or it is found in the mid-part of the myocardium (229). The majority of the studies differentiating ICM from NICM exclude patients with forms of cardiomyopathy other than idiopathic dilated cardiomyopathy, such as hypertrophic cardiomyopathy (HCM) or that caused by myocarditis or infiltrative disease. LGCE can also help differentiate these types of cardiomyopathy from other forms due to distinct patterns of LGCE and underlying morphology of the LV (230). For example, extensive work by Moon *et al.* has shown that information regarding the aetiology and subsequent prognosis can be gained when using this technique in HCM, where the pattern of LGCE is typically confined to the ventricular septum (233) (Figure 1.7). LGCE in patients with HCM is associated with more severe forms of the disease such as those with LVSD and its presence confers adverse prognosis and an increased risk of ventricular arrhythmias and sudden death. The technique of LGCE has been shown to be accurate when compared to autopsy and histological specimens in animal models (234) and humans (235) and is more accurate than SPECT imaging (236) with comparable accuracy to PET imaging (237-238) for the assessment of myocardial viability. Such has been the success of this non-invasive imaging technique that it has now been established as a Class 1 indication for the assessment of myocardial viability in ICM, the differentiation of ICM from NICM and in the assessment of both aetiology and prognosis of NICM (206,238).

CMR is thus an accurate technique for the diagnosis and assessment of LV morphological abnormalities, gives unique insight into the underlying aetiology of any identified LV abnormality and can identify ICM without the need for invasive coronary

angiography. It would therefore seem ideally suited to aid the investigation of LV abnormalities and their association with CAD in patients with ESRF.

1.10 Aims of this Thesis

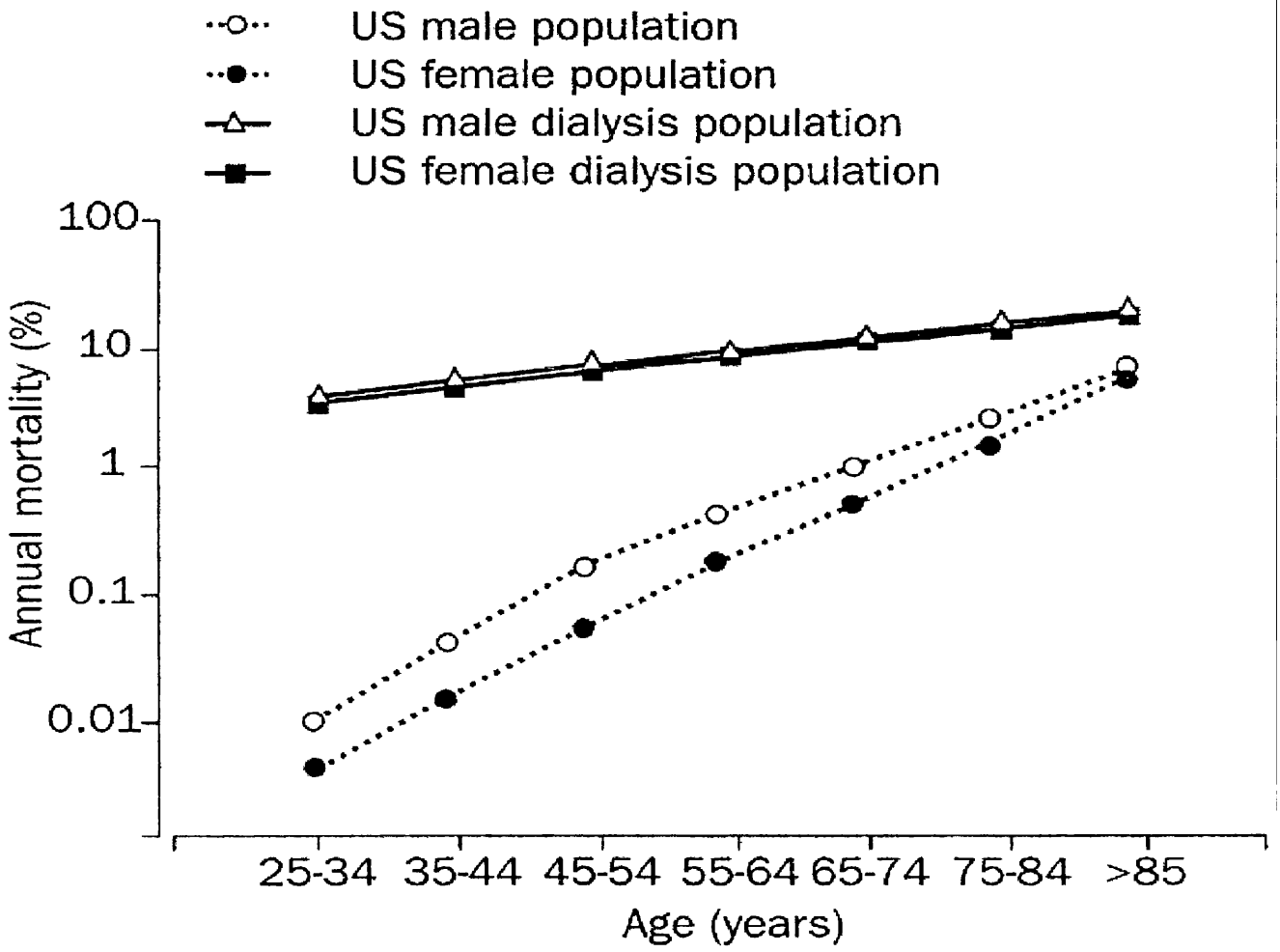
With the expansion of dialysis programmes, demand for renal transplantation continues to increase and CVD is now the most common cause of death in both patients awaiting renal transplantation and in those with a functioning renal allograft. It therefore follows that to further improve the benefits of renal transplantation, better diagnosis and treatment of CVD is mandatory.

LV abnormalities are the strongest independent predictors of CV outcome in this population. Although it is known that LV abnormalities, especially LVH, are prevalent in patients on RRT, the current methods of assessment of such abnormalities are inaccurate, especially in this population and thus it is unknown whether targeting LVH or other LV abnormalities confers improved outcome to patients with ESRF and the relationship of LV abnormalities and CAD is poorly defined. CMR is now an established imaging modality in clinical cardiology and the standard of reference for the measurement of LV structure and function. As yet, CMR has not been used in the investigation of LV abnormalities and IHD in patients with ESRF. The aims of this thesis are therefore as follows;

- To identify the prevalence of LV abnormalities in patients awaiting renal transplantation using CMR.

- To identify the clinical correlates and potential determinants of LV abnormalities identified using CMR in order to identify opportunities for future interventional trials.
- To study the natural history of LV abnormalities whilst patients wait for renal transplant with CMR.
- To examine the relationship between LV abnormalities and anaemia in patients with ESRF using CMR
- To assess the usefulness of BNP in identifying patients with LV abnormalities defined by CMR
- To investigate the relationship between CAD and LV abnormalities using a combination of LGCE and cine CMR.
- To assess the strength of LV abnormalities defined by CMR to predict the outcome of patients awaiting renal transplantation

Graph 1.1 CV mortality rates of US dialysis patients compared to that of the normal population (17)



Graph 1.2 Adjusted relative risk of death among recipients of a first cadaveric renal transplant compared to those remaining on the waiting list (1)

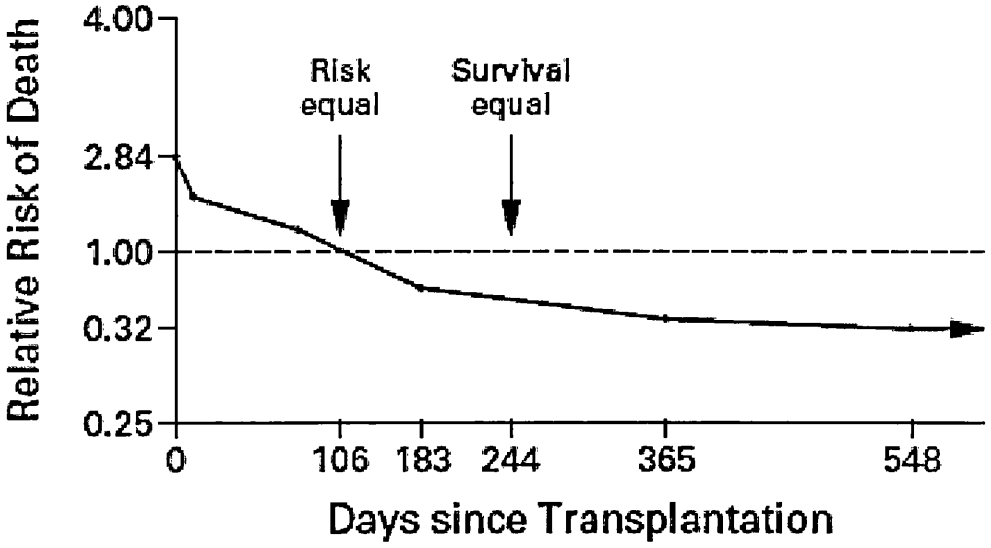


Table 1.1 Traditional and non-traditional risk factors for CVD in patients with progressive renal failure (37)

Traditional Risk Factors	***Non-traditional Risk Factors***
Older age	Albuminuria
Male sex	Hyperhomocysteinaemia
Hypertension	Anaemia
High total cholesterol	Abnormal calcium/phosphate metabolism
High LDL cholesterol	Extracellular fluid volume overload
Low HDL cholesterol	Oxidative stress
High triglycerides	Inflammation
Diabetes	Malnutrition
Smoking	Thrombogenic factors
Family history of premature IHD	Altered nitric oxide/endothelin imbalance
Physical inactivity	Lp(a) lipoprotein
Left ventricular hypertrophy	

Table 1.2 Prevalence and pattern of dyslipidaemia at varying stages and types of progressive renal failure (53)

	Total Chol >240mg/dl	LDL Chol >130mg/dl	HDL Chol <35mg/dl	Trigs >200 mg/dl
General population	20%	40%	15%	15%
CRF Stage 1-4 +nephrotic syn	90%	85%	50%	60%
CRF Stage 1-4 -nephrotic syn	30%	10%	35%	40%
CRF Stage 1-4 + renal transplant	60%	60%	14%	35%
CRF Stage 5 on HD	20%	30%	50%	45%
CRF Stage 5 on PD	25%	45%	20%	50%

Graph 1.3 Mortality rate of diabetic (dashed line) and non-diabetic (solid line) patients commencing RRT (64)

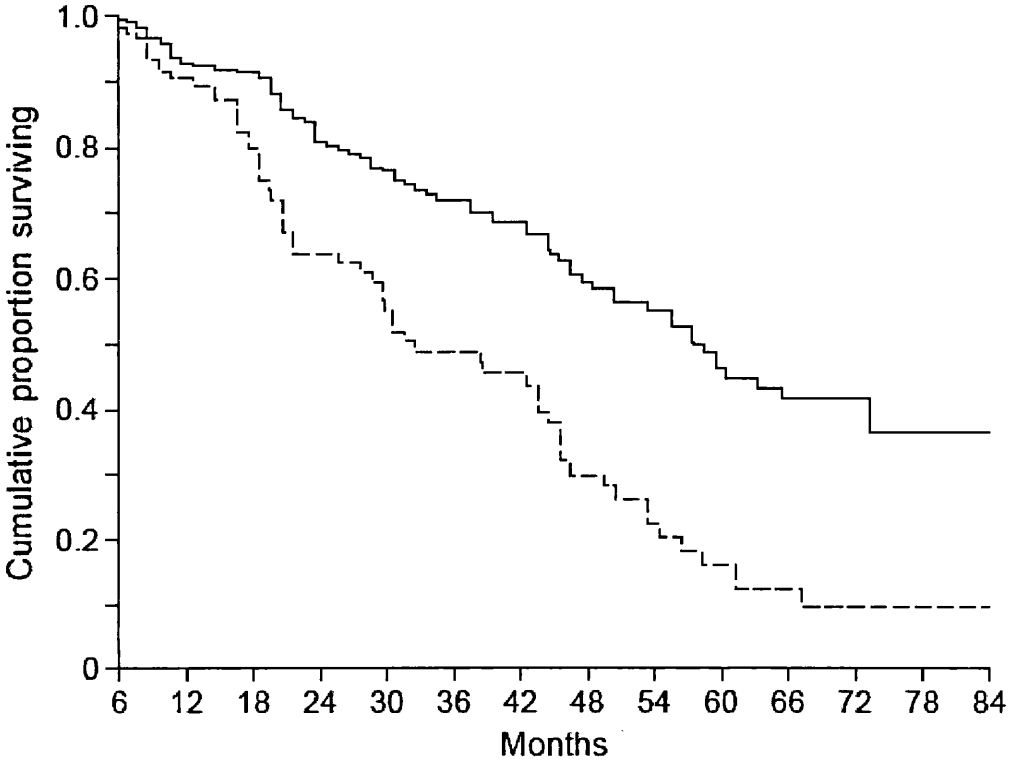


Figure 1.1 Piechart demonstrating the prevalence of LV abnormalities in 433 patients commencing RRT, defined using echocardiography (69)

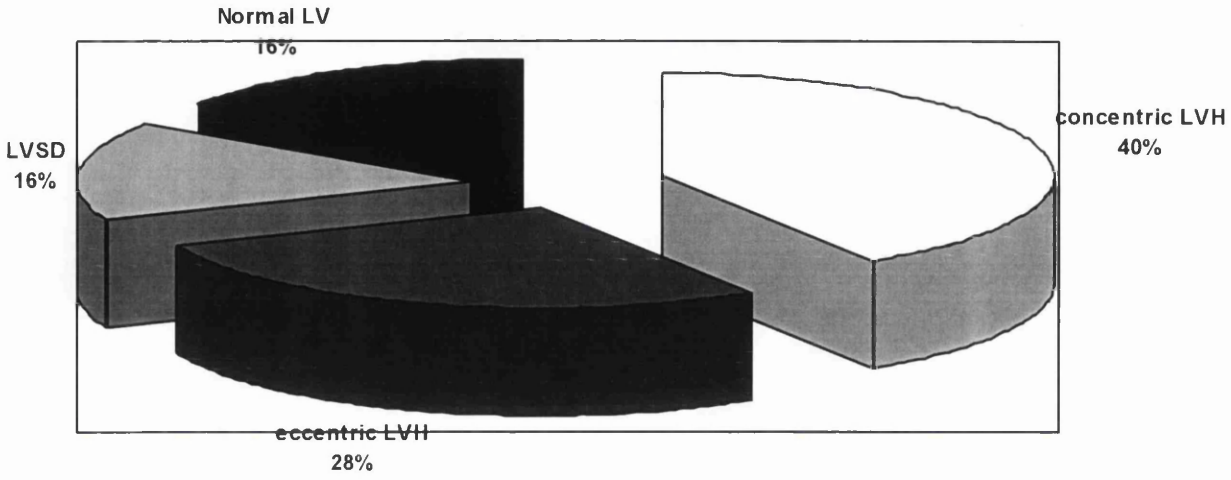


Figure 1.2 Actions and physiological effects of natriuretic peptides (121)

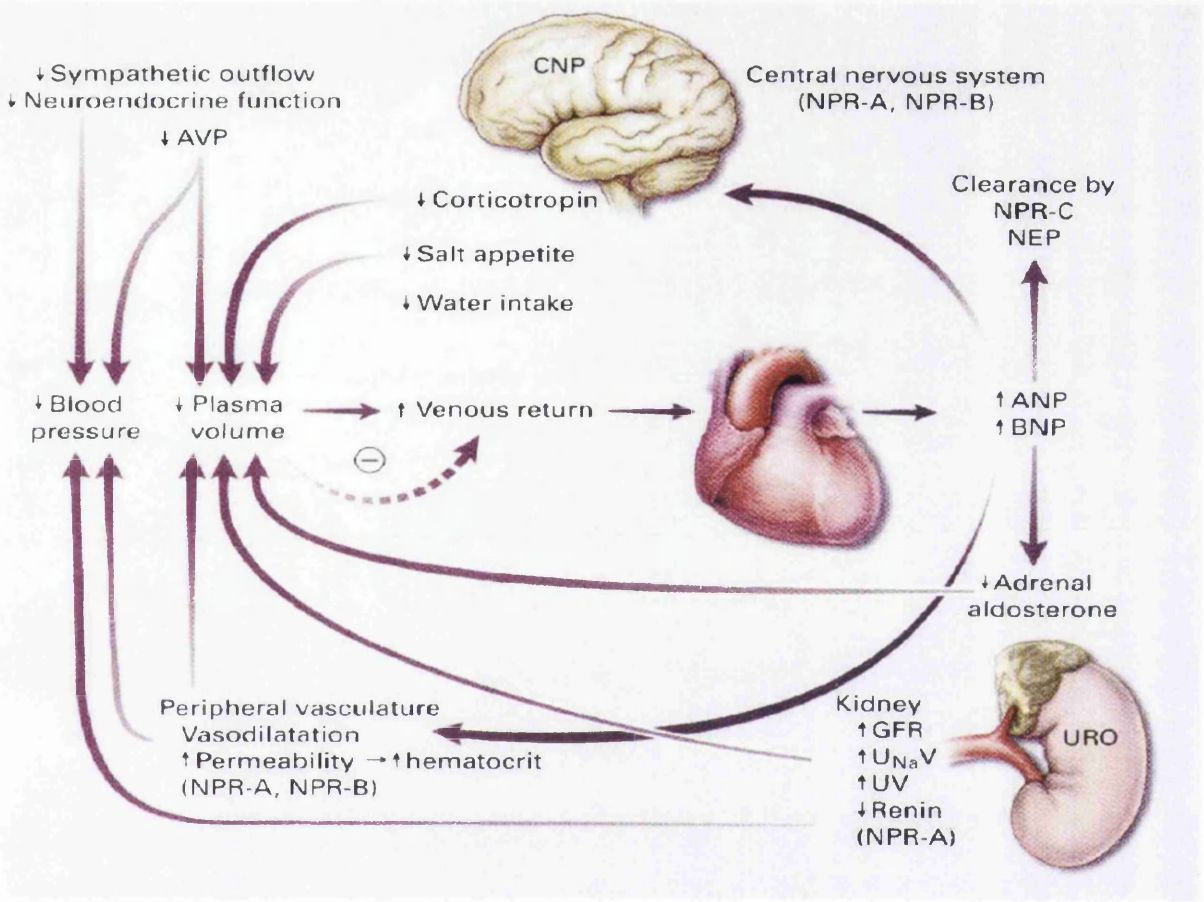
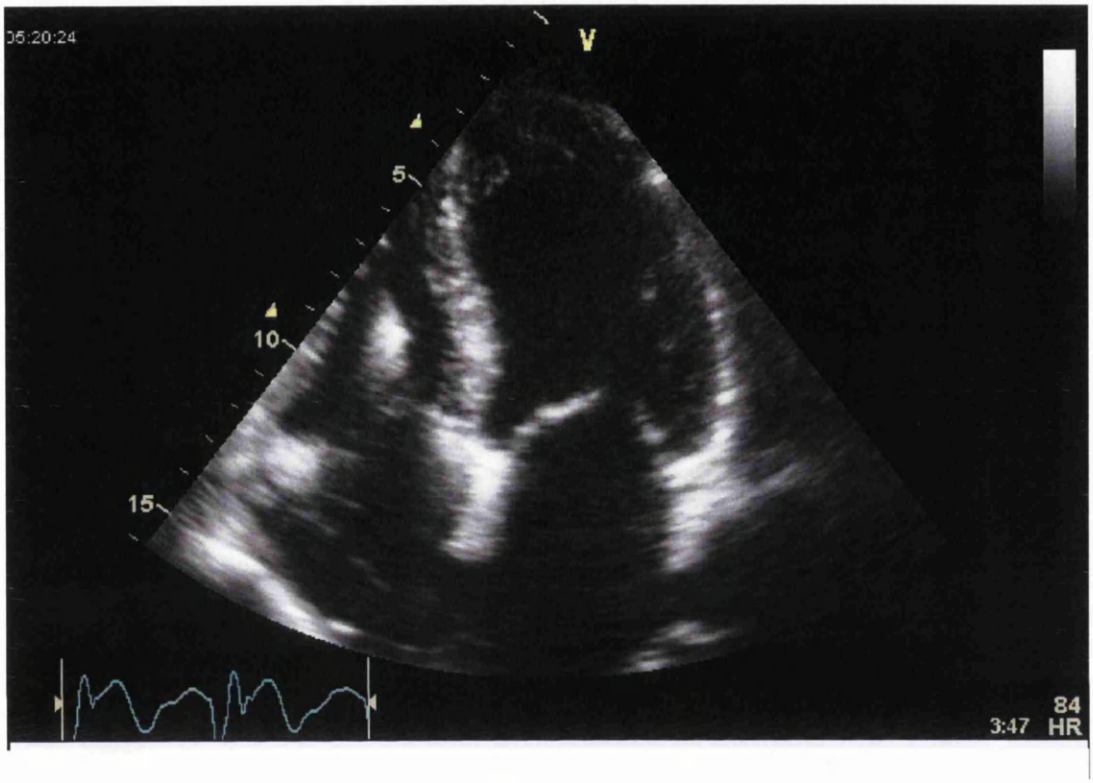


Figure 1.3 Typical 4-chamber and parasternal long axis views using 2-dimensional echocardiography in a patient on RRT with LVSD (Dashed line depicts correct placement of M-mode cursor)



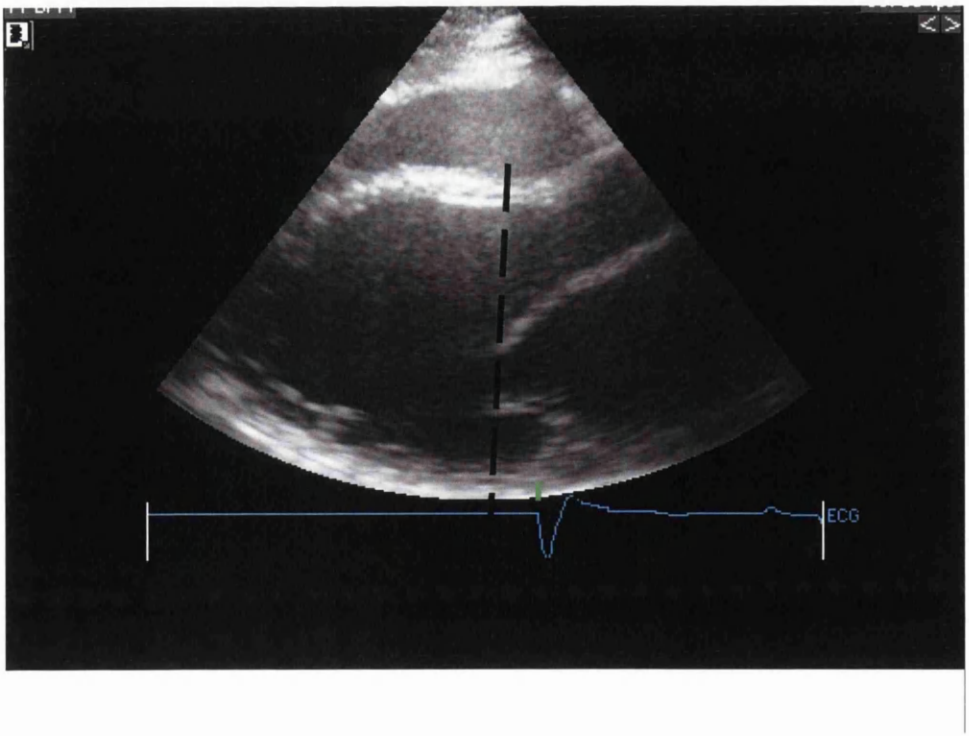


Figure 1.4 Echocardiographic M-mode images and demonstration of measurement of LV parameters for Troy and Pombo (Standard), Penn and ASE conventions in a normal subject

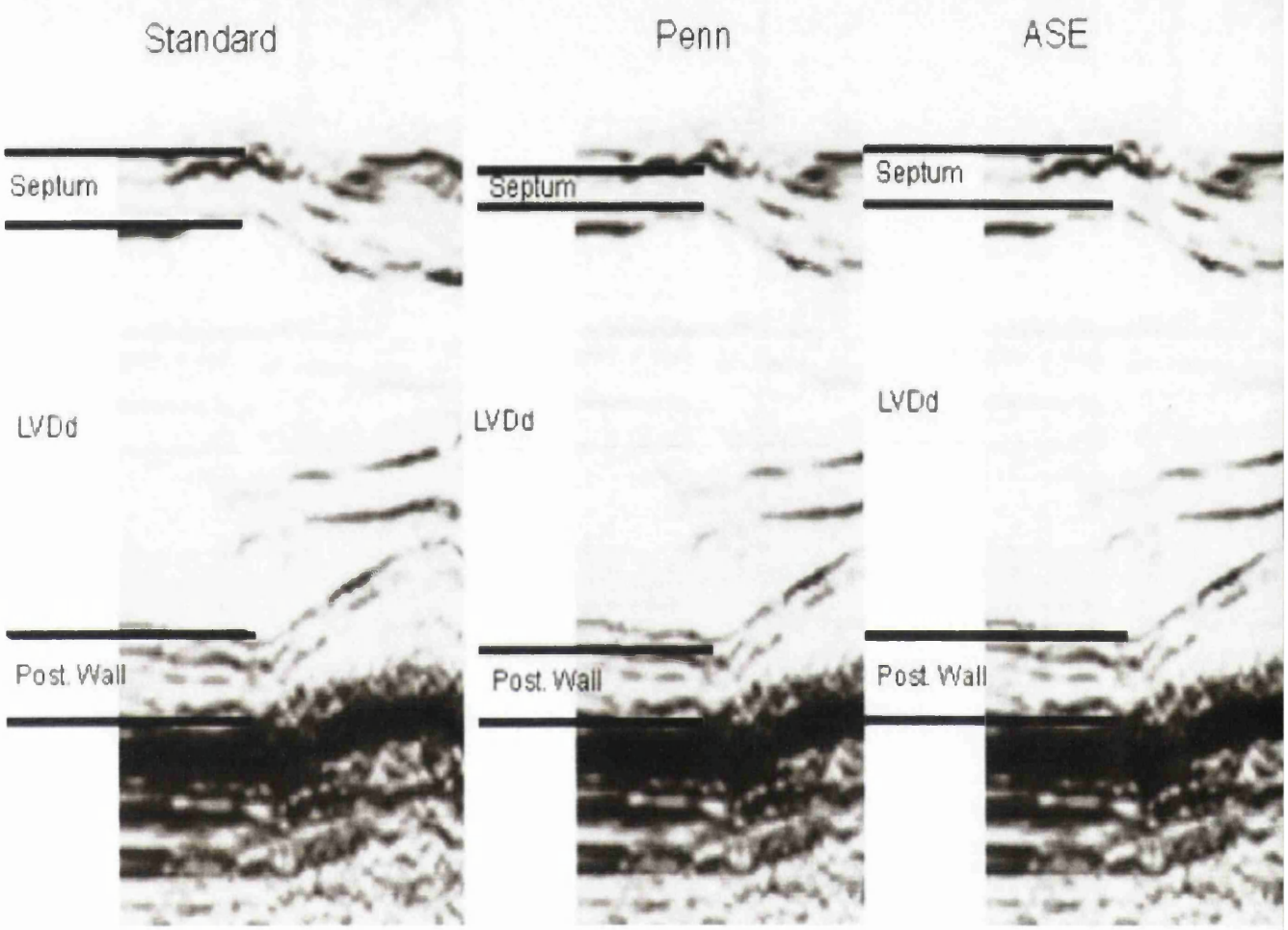


Figure 1.5 Typical subendocardial pattern of late gadolinium contrast enhancement associated with myocardial infarction in a patient post septal myocardial infarction

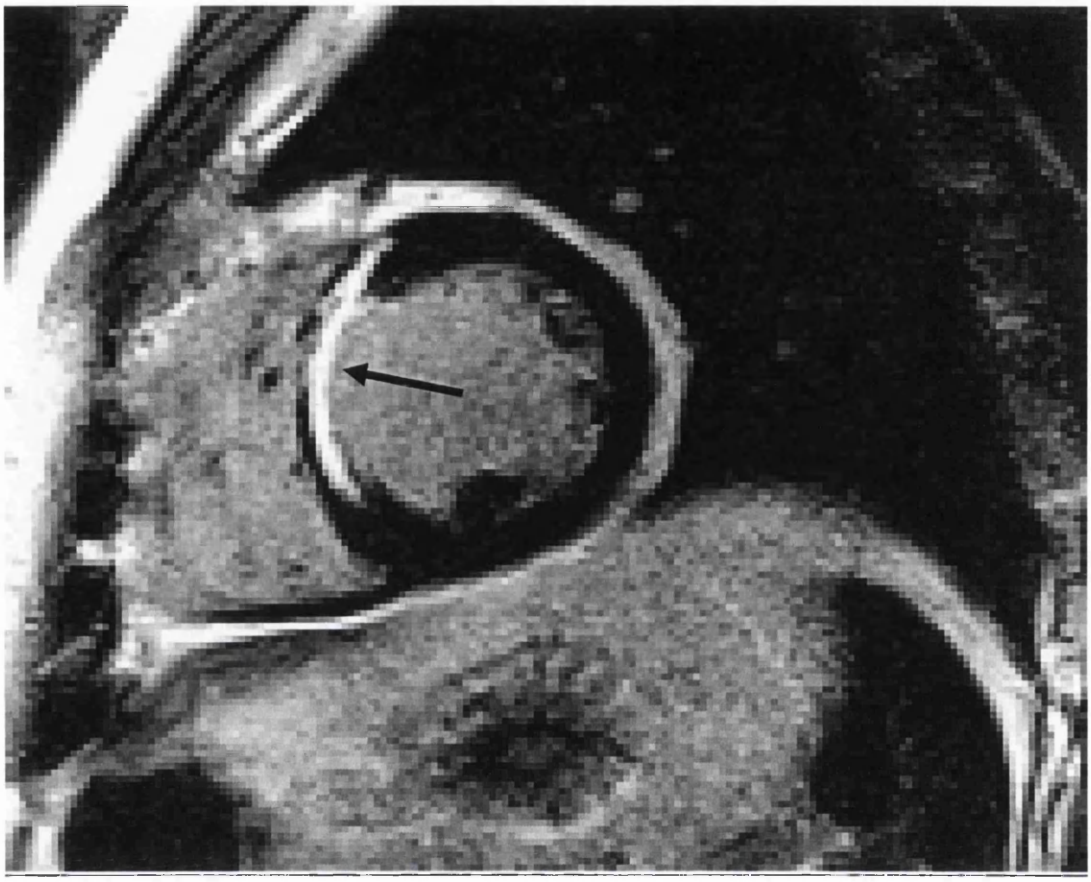


Figure 1.6 Basis for contrast enhancement with gadolinium chelates in damaged myocardium, imaged using CMR (224)

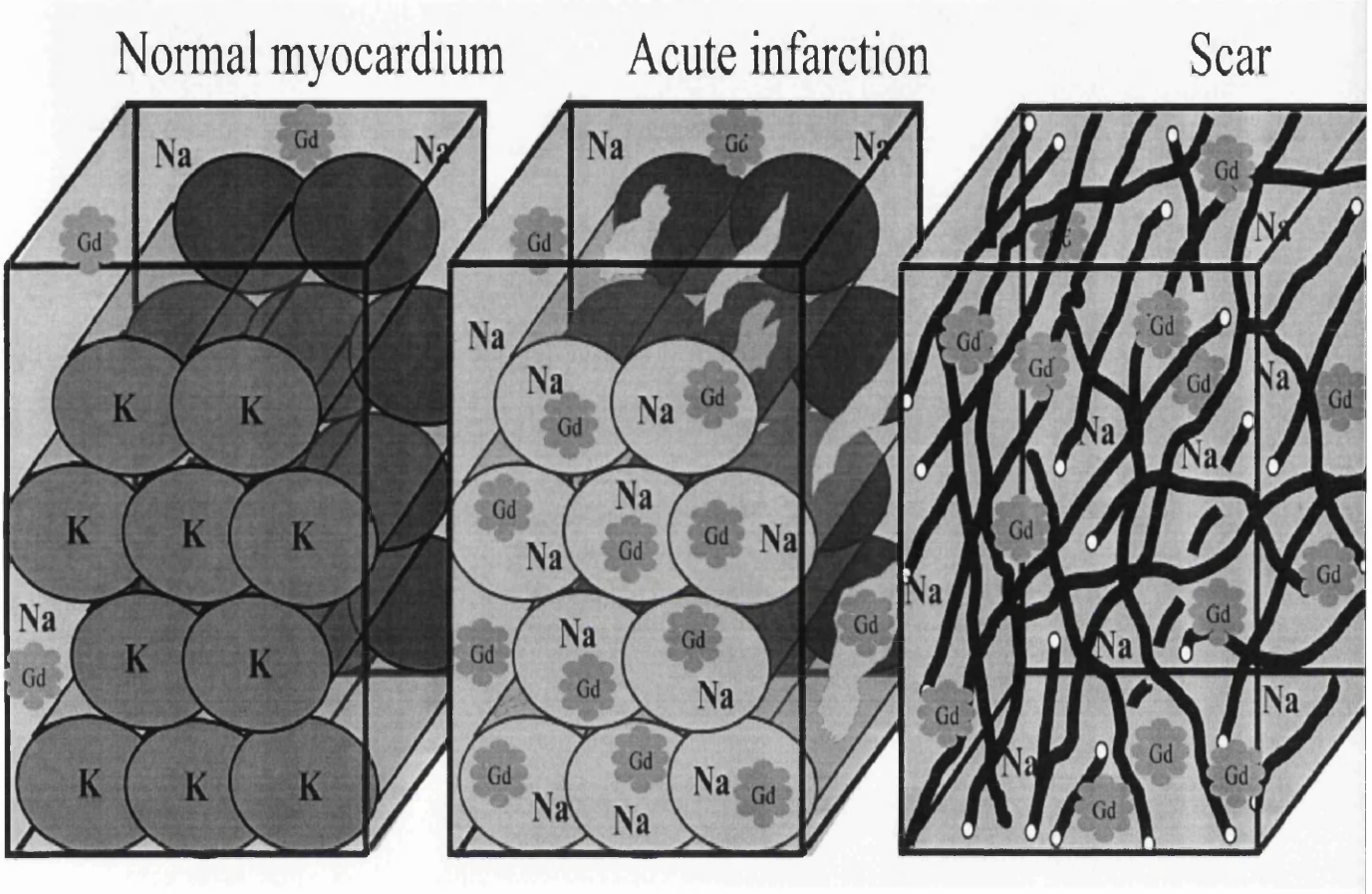
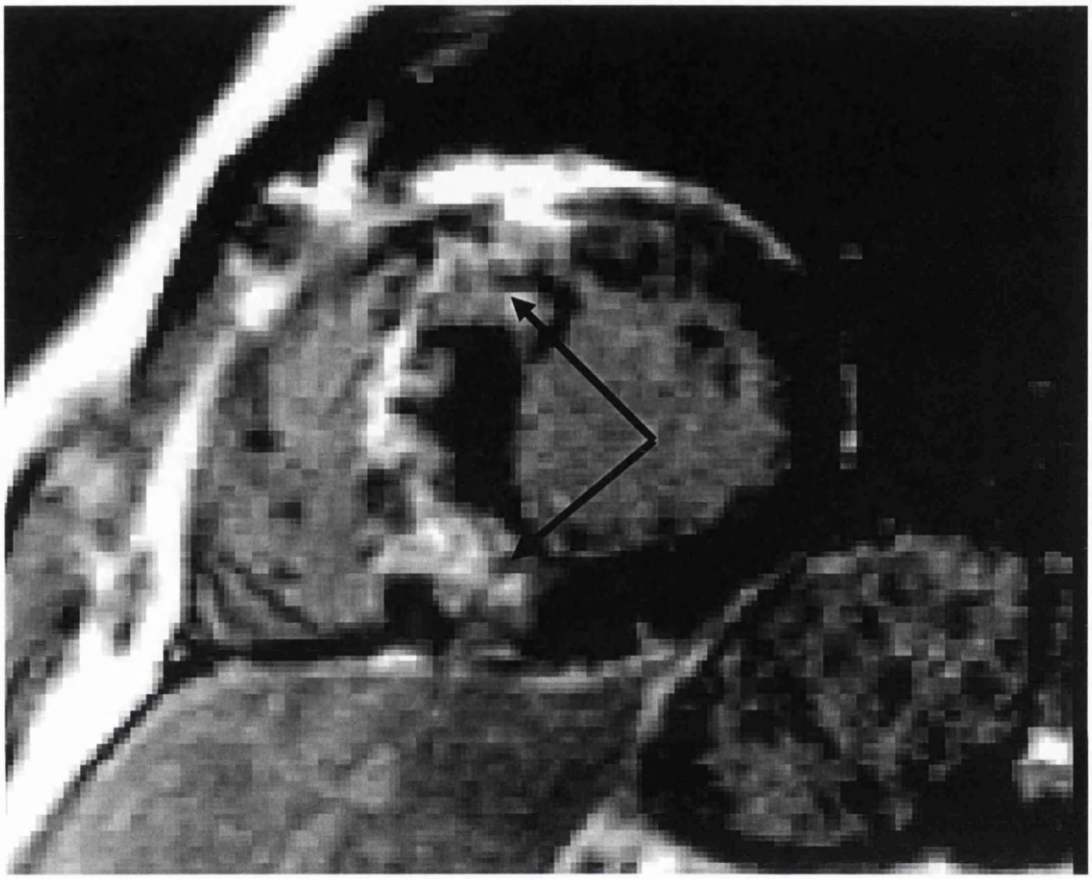


Figure 1.7 Patchy septal distribution of LGCE in a patient with genetic hypertrophic cardiomyopathy



Chapter 2

Methods

2.1 The study population- Sampling and Invitation process

All patients with ESRF on the West of Scotland renal transplant waiting list in January 2001, were invited to participate in the study by letter. Those who initially did not respond were contacted by a second letter. There were 55 patients on the waiting list at that time, of which 44 attended for screening. Thus 80% of the waiting list attended for screening and the major reason for the 11 patients declining screening was the distance involved in travelling to the Western Infirmary for screening. The remainder of the patients entering the study were recruited from the renal transplant assessment clinic at the Western Infirmary, Glasgow between January 2001 and August 2002. All patients gave informed consent and signed the consent form approved by the local Ethics Committee.

A total of 154 patients were screened for the study. Three patients could not undergo CMR scanning due to contraindications regarding ferromagnetic objects (one patient had previous surgery and clipping for subarachnoid haemorrhage, one patient had a ventriculo-peritoneal shunt for hydrocephalus and one patient had a foreign body from a previous accident. Three patients could not tolerate the scan due to claustrophobia and therefore in total 4% of patients could not undergo CMR scanning. The study cohort therefore consisted of 148 patients.

2.2 Basic protocol

Patients attended for screening on a post dialysis day, if using haemodialysis as mode of RRT, and patients using PD were studied at their 'dry weight' according to clinical charts. The screening protocol followed is displayed in Flowchart 2.1 and apart from CMR imaging is the protocol in place for CV screening for the West of Scotland transplant assessment clinic. Patients initially filled in a questionnaire to obtain details of past renal and other medical history, medication taken, standard CV risk factors (hypertension, hyperlipidaemia, diabetes, smoking history, family history), CV co-morbidity and the presence of any symptoms suggestive of CVD. IHD was defined as a history of angina for which regular medication was taken, a previous history of AMI, PCI or CABG or previously documented CAD at angiography. CHF was defined as previously documented LVSD. If the patient was unable to remember any of the required information, this data was obtained from the West of Scotland renal database with the patient's consent.

The patients then underwent physical examination. Pulse rate and BP were recorded as well as auscultation of heart and lungs and clinical assessment of peripheral pulses.

A 12-lead ECG was obtained and blood samples were taken after the patient had been recumbent for 20 minutes, followed by a CMR scan. After CMR scanning the patients underwent exercise tolerance testing (ETT).

If a patient was found to have LVSD or had a high risk treadmill test, they were referred for coronary angiography. If the patient did not perform adequately on treadmill testing or the test was inconclusive, they were referred for nuclear stress perfusion imaging.

Again, if the nuclear perfusion scan showed a reversible perfusion defect, the patient was referred for coronary angiography (Figure 2.1).

Patients reattended after at least 6 months for repeat CMR scanning. Patients were excluded from repeat scanning if they had undergone renal transplantation in the preceding 6 months. Repeat BP measurement and blood sampling were performed and a proportion of patients had a more detailed CMR scan with LGCE. Patients gave informed consent to the more detailed CMR study and signed the consent form approved by the local Ethics Committee.

Patients were thereafter followed up for 4 years to detail all cause mortality. Patient outcome was monitored via the West of Scotland renal database.

2.3 Pulse and blood pressure measurement

Pulse rate and rhythm were assessed both clinically and by resting 12-lead ECG. BP was taken after 20 minutes in the recumbent position, before blood sampling, using an automatic Critikon Dinamap Plus Vital Signs Monitor. BP was monitored during and after ETT and was again measured at the end of the screening visit. The mean BP from the initial BP check and that at the end of the study visit was used for subsequent analysis.

2.4 Blood Sampling

Venous blood was sampled after the patient was recumbent for 20 minutes. Blood was taken for the analysis of urea and electrolytes, full blood count, glucose, total cholesterol, CRP and BNP. All analysis except for BNP measurement was carried out by the clinical

biochemistry and haematology laboratories in the Western Infirmary. The venous blood sample taken for BNP was collected in chilled tube containing trasylol (50u/ml). It was then centrifuged at 3000g for 10 minutes at 4C to obtain separated plasma which was stored at -80C until batch analysis. This was carried out in the University of Glasgow biochemistry department using a commercial BNP assay kit (Shionoria BNP kit, Shionogi, Japan). The limit of detection of this kit is 1pg/ml (0.29 pmol/L) and the co-efficient of variance for within assay and between assay variation was <2.7% and <4.2% respectively.

2.5 Electrocardiogram

A 12-lead ECG was acquired prior to ETT. This was acquired using a Siemens Megacart ECG system (Siemens Medical Systems, Erlangen, Germany) and the ECG was recorded at 22mm/sec and 1mV/cm standardization. Heart rate and rhythm was recorded and the presence or absence of pathological Q waves and ST changes. Pathological Q waves were defined as Q waves more than 1mm width and 3mm depth and ST shift was defined as any resting ST depression.

The ECG criteria used to define LVH was the Cornell product (240-241). The Cornell voltage (242) is calculated by multiplying the voltage of the R wave in lead aVL by the voltage of the S wave in lead V3 thus; RaVL x SV3. The Cornell Product is calculated by multiplying the Cornell voltage by the QRS duration in milliseconds ([RaVLxSV3]xQRS). The partition coefficient used to define LVH from the ECG was >2592mV.ms for males and >2610mV.ms for females (241).

2.6 Exercise Tolerance Testing

All patients were asked to undergo ETT. This was carried out on a Marquette CASE 15 ETT system treadmill machine using a standard Full Bruce protocol which was first published in 1963. This protocol is conducted in up to 7 stages each lasting 3 minutes. Stage 1 is the equivalent of 4.6 metabolic equivalents of work (METS), where one MET is the amount of oxygen consumed at rest. (At rest 1 MET= 3.5ml of oxygen/Kg/min). Stage 1 is conducted at a speed of 1.7mph and a gradient of 10 degrees. Each stage thereafter increases in speed and grade.

Patients had continuous 12-lead ECG monitoring during and after exercise and BP was recorded at the end of each stage during the test and every two minutes after the test until BP returned to baseline. Symptoms of chest pain and breathlessness were recorded during the test as was heart rate achieved and total exercise time. Patients were asked to exercise until 85% of target heart rate was achieved (calculated as 220-age of patient) and to exercise for at least 6 minutes and 30 seconds. The test was considered high risk if there were >2mm of horizontal or down sloping ST depression in 2 or more contiguous leads, a positive response within 6 minutes or exertional hypotension. The test was considered intermediate risk if the patient developed symptoms of chest pain during the procedure without ECG changes and the test was considered inconclusive if the patient did not reach target heart rate and/or did not exercise for 6 minutes 30 seconds.

2.7 Cardiovascular Magnetic Resonance Imaging

All patients in the study underwent CMR scanning on at least one occasion. This was carried out on a 1.5 Tesla Siemens, Sonata whole body system (Siemens Medical

Systems, Erlangen, Germany), equipped with a circularly polarized phased-array body coil. Images were obtained using retrospective ECG gating and imaging sequence was triggered on the R wave.

An initial series of scout images were obtained using a true fast imaging with steady state precession (TRUE FISP) pulse sequence in the coronal, transverse and oblique-sagittal views. These scout images were used for planning an initial vertical long axis (VLA) pilot image and using this VLA pilot, a horizontal long axis (HLA) pilot was planned. Using the VLA and HLA pilots a series of three short axis (SA) pilots were obtained and using this set of pilot images, TRUE FISP breath hold cine images in the HLA, VLA and 3-chamber views were obtained. The HLA/4-chamber view (Figure 2.2) and the VLA/2-chamber view in the end-diastolic frame were used to position the complete stack of short axis, TRUE FISP, breath hold, cine images from the base of the LV to the apex (Figure 2.3) and this short axis stack was used in the analysis of LV mass, volumes and function. The most basal image plane was positioned close to the transition of the LV myocardium to the mitral valve leaflets thus covering the most basal part of the LV.

The images were acquired using a standardized protocol of 8mm slices with 2mm gap between slices and number of images depended on length and size of ventricle (Range of 8-13 slices). TRUE FISP sequences rephrase the transverse magnetization (instead of spoiling it) after phase encoding and readout. This results in an improved blood-myocardium contrast, being dependant mainly on the tissue to blood T1/T2 ratio and not on through plane blood flow. Thus, the following standardized system parameters were used;

- repetition time (TR) = 3.14ms

- echo time (TE) = 1.6ms
- flip angle (α) = 60°
- voxel size = 2.2x1.1x8.0mm
- Field of View (FoV) = 340mm

The duration of the CMR scan was on average 20 minutes.

A proportion of patients also underwent an extended scanning protocol involving the administration of a 0.2mmol/Kg bolus of Gd-DTPA, which is a gadolinium based extracellular contrast agent. Patients undergoing the extended scan protocol had a 16 gauge venflon inserted into a suitable vein in the antecubital fossa prior to scanning. Further images were acquired 10 minutes after administration of Gd-DTPA using a breath hold, segmented, turbo fast low angle shot (FLASH) gradient-echo pulse sequence technique with an initial inversion pre-pulse (180°). The pre-pulse delay (inversion time) was chosen so there was no/minimal longitudinal magnetization in the normal myocardium which therefore appeared dark (nulled). Any remaining contrast agent in the myocardium due to delayed wash-in and wash-out kinetics through infarcted or fibrotic myocardium, exhibited a faster T1 relaxation and therefore appeared bright.

For this sequence the following standardized system parameters were used;

- TR = 11.6ms
- TE = 4.3ms
- α = 20°
- voxel size = 2.2x1.1x8.0mm
- FoV = 300mm

Inversion time was chosen on an individual patient basis.

Image analysis was carried out on ARGUS software (Siemens, Erlangen, Germany). Patients underwent initial screening echocardiography to ensure there was no significant valvular heart disease, which may have affected results for LV mass and volumes. For the analysis of mass and volumes, end-diastole (ED) was defined as the first temporal frame directly after the R wave of the ECG. End-systole (ES) was defined as the temporal frame at which the image showed the smallest LV cavity and was typically 240-320ms after the R wave. LV epi- and endocardial contours were manually traced around the ED frame and the ES frame for each of the short axis slices encompassing the LV. The papillary muscles were included in the mass calculation and excluded from the volume calculation. EDV and ESV were calculated by the summation of the product [area x slice distance] for all slices.

Stroke volume (SV) was calculated using the formula; SV=EDV- ESV

EF was calculated using the formula; EF = (SV/EDV) x 100%.

CO was calculated by multiplying SV and heart rate.

The LV ED mass was obtained by multiplying the volume of LV muscle by the specific weight of muscle tissue, which is $1.05 g/cm^3$.

The global LV measures were indexed for BSA thus;

BSA (g/m^2) = Weight 0.425 x Height 0.725 x 0.007184

A proportion of the images (10 scans) were analysed by a second observer for the calculation of inter-observer variability and 10 scans were analysed on two separate occasions in a random order by the first observer for calculation of intra-observer

variability. Both were found to be within published ranges at 7.4% and 5.8% respectively (213,216).

Analysis of the LGCE images was carried out on ARGUS software by two blinded observers (John Foster, CMR physicist and Tracey Steedman, CMR radiographer). The presence of myocardial fibrosis was indicated by the presence of LGCE. Images were obtained in long-axis in the HLA, VLA and 3-chamber view and in the SA orientation using the same slice positions as the cine SA images obtained for functional analysis. Images were assessed initially for the presence or absence of LGCE and in those patients that displayed LGCE the pattern of enhancement was divided into either 'patchy' LGCE, not consistent with coronary artery disease (CAD) or 'discrete' LGCE consistent with CAD.

Patients were classed as having LGCE if two or more contiguous SA slices showed evidence of LGCE and the corresponding area on either the routine long axis images or a further long axis image planned through the area of LGCE on the SA slices. If artefact was suspected on any of the images, the phase-encoding direction was changed and if the area of LGCE persisted, it was regarded as true LGCE.

2.8 Nuclear stress perfusion scanning

Patients who were classed as requiring further non-invasive assessment for reversible ischaemia, if treadmill testing was inconclusive or not possible, were placed on the waiting list for out-patient nuclear stress perfusion (SPECT) scanning at the Western Infirmary. The scans were carried out on a 3000 XP triple headed gamma camera with attenuation correction facility, using technetium Tc-99m (tetrofosmin) as the radioactive

perfusion agent and dipyridamole as the stress agent in combination with bike exercise if possible. Dipyridamole was administered as a bolus injection with a dose of 0.56mg/Kg over 4 minutes. In patients for whom dipyridamole was contra-indicated (i.e. those with reversible obstructive airways disease) dobutamine was administered as the stress agent. Dobutamine infusion was commenced at 10μg/kg/min and increased in increments of 10μg/kg/min every 3 minutes up to a total of 40μg/kg/min or until target heart rate was achieved.

Images were analysed by the single physician responsible for reporting nuclear stress perfusion scans for the hospital and were graded initially as a normal stress perfusion scan or an abnormal stress perfusion scan. Those that had an abnormal scan were divided into those with a fixed perfusion defect or a reversible perfusion defect. Those that had both a fixed and stress perfusion defect were placed in the reversible defect category. The scans were carried out within six months of the original screening visit.

2.9 Coronary angiography

Patients who were classed as requiring coronary angiography were placed on the waiting list for out-patient coronary angiography at the Western Infirmary. The angiograms were carried out by a single operator via the femoral route and the patients undergoing coronary angiography were classified as having normal coronary arteries, mild/moderate CAD (defined as the presence of coronary atheroma but no single coronary plaque stenosis of more than 70%) and those with and stenosis over 70% were considered to have severe CAD.

Figure 2.1 Screening protocol for CV risk assessment in renal transplant candidates

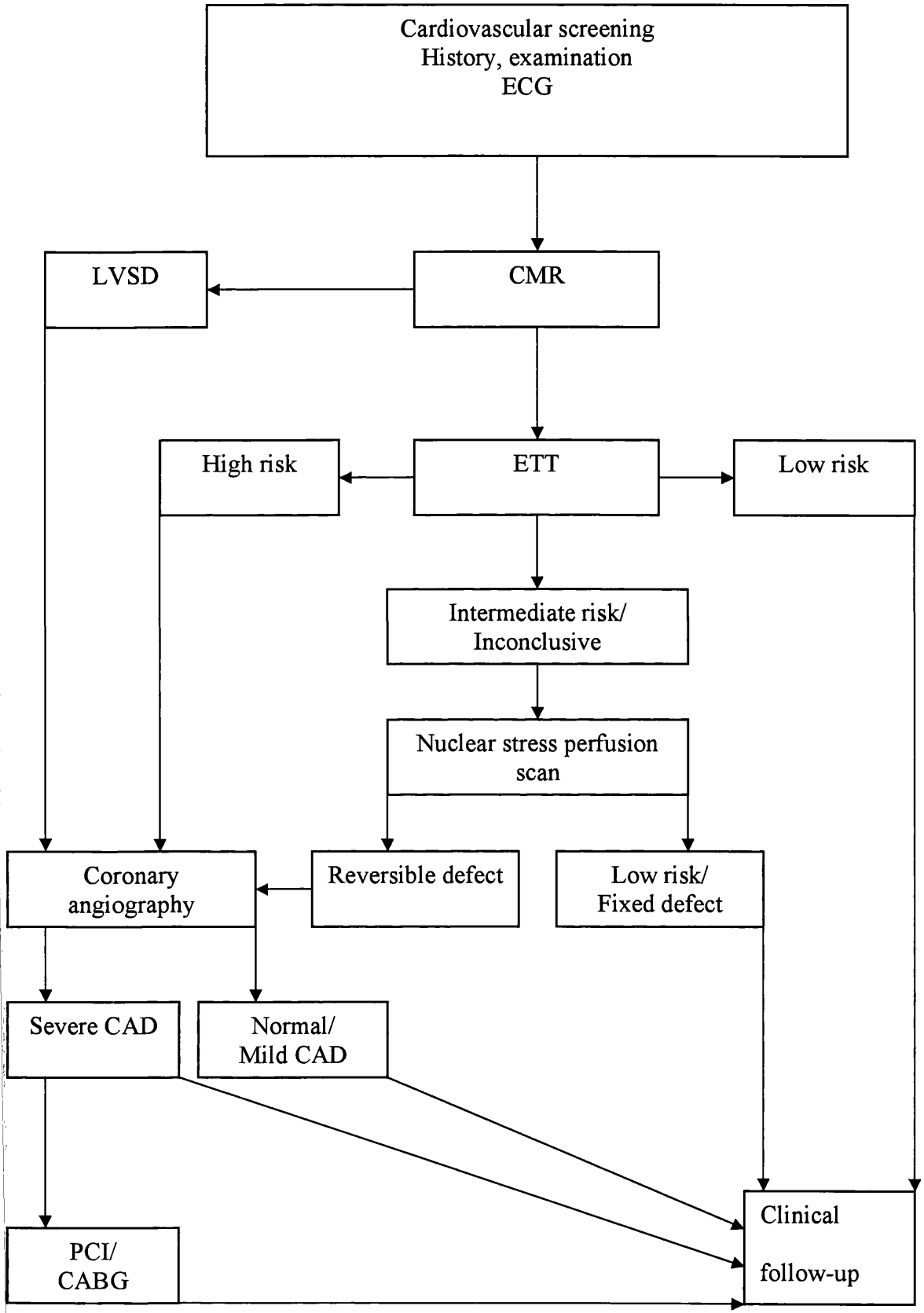


Figure 2.2 Horizontal long axis CMR image and planned short axis slices

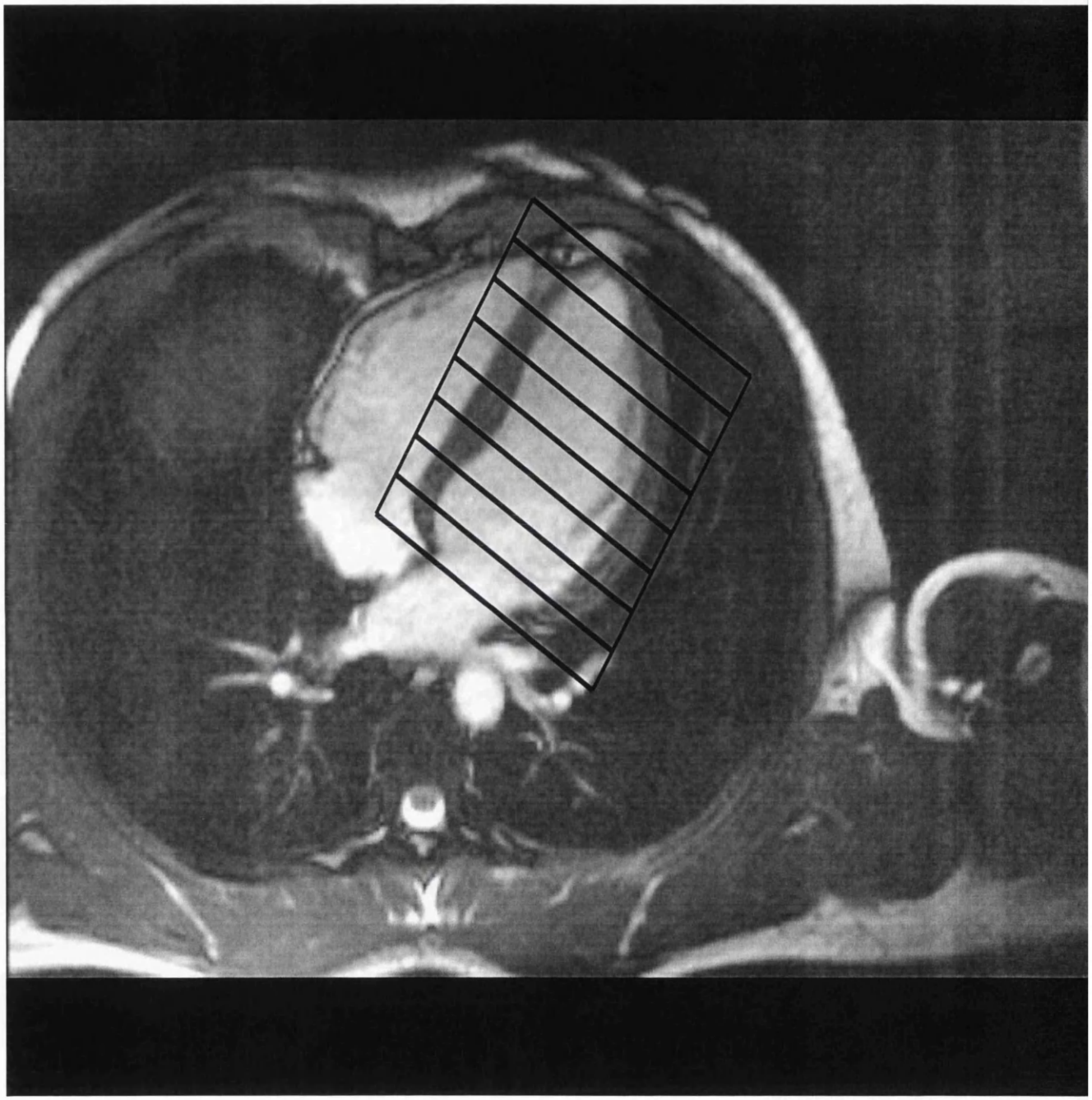
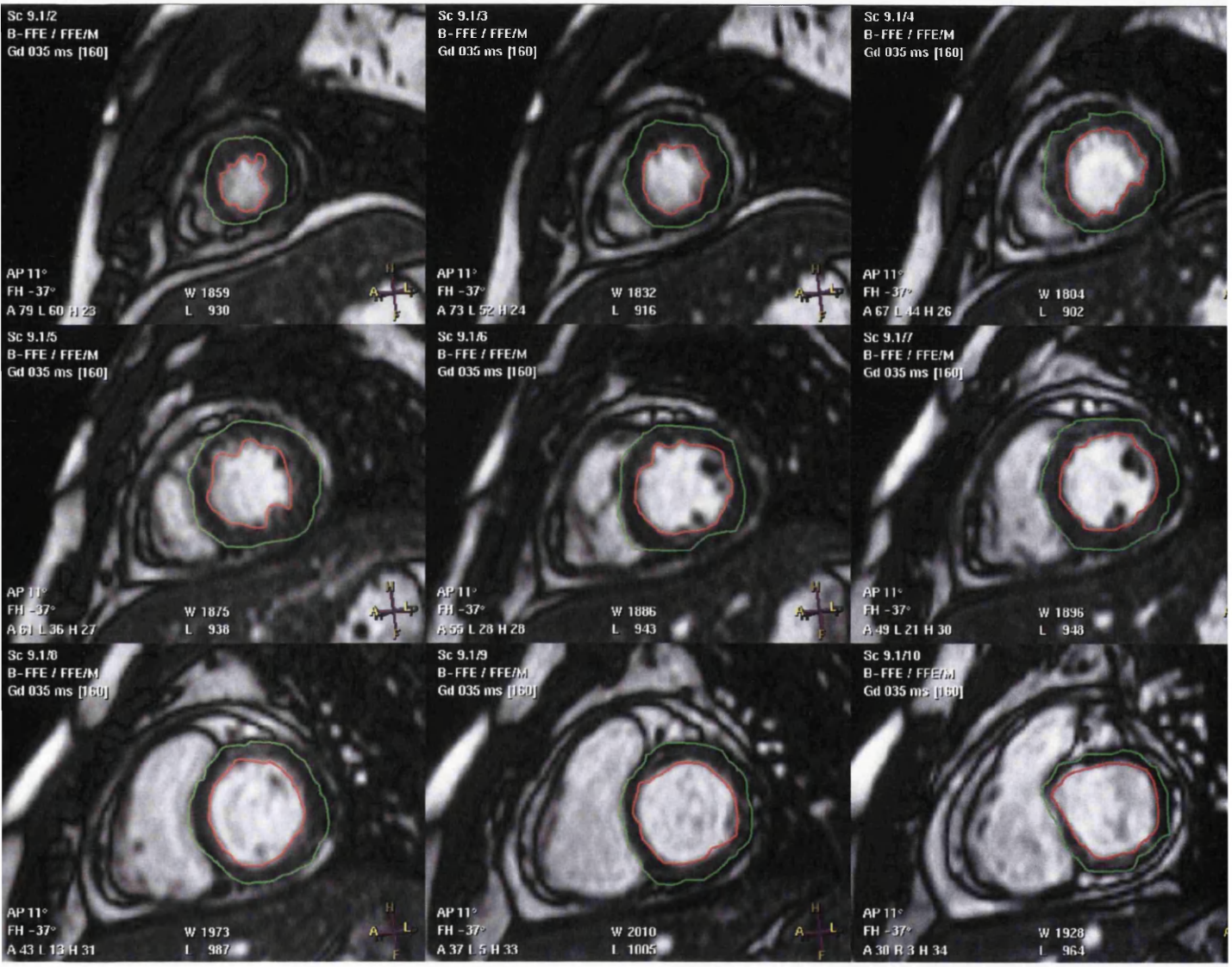


Figure 2.3 Corresponding short axis stack used for calculation of LV mass, volumes and function with endocardial (red) and epicardial (green) contours used in analysis of LV mass, volumes and function



Chapter 3

Characteristics of the Study Population and the Risk Factors for Cardiovascular Disease

3.1 Introduction

Applying current European Best Practice Guidelines (243) to the selection of patients suitable for renal transplantation, results in substantial selection of healthier patients compared to those remaining on RRT. Candidates who undergo transplantation are younger, more likely to be male, have non-diabetic renal failure and have less co-morbidity than patients on RRT who are not considered suitable for transplantation (1,3). In the UK, Oniscu *et al.* (3) studied 1736 patients listed for renal transplant in Scotland over a 10 year period between 1989 and 1999. Average age of patients was 46.6+/-14.1 years, 20% had a prior history of IHD and the proportion of diabetic patients was 14.6%. More recently Sharma *et al.* (87) studied 203 transplant candidates between 1996 and 2001. Average age of this London based cohort was 47+/-12 years, the proportion of patients with a history of IHD was 4% and the proportion of diabetics was 21%.

Guidelines also exist for the assessment of CVD in patients being considered for transplantation and for the treatment of CV risk factors such as hypertension and hyperlipidaemia in all patients with ESRF. In the UK, the Renal Association have published guidelines stating that patients over the age of 49, in addition to patients with a history of diabetes, previous IHD, other vascular disease or CHF should be considered at high CV risk and undergo stress testing prior to listing for transplantation (244). Furthermore, the Renal Association also advise that risk factors such as hypertension,

hyperlipidaemia and smoking should be aggressively targeted in patients on RRT and those patients with a history of IHD should be on secondary preventative therapy as recommended for the general population (245).

Despite similar advice from renal associations in other countries (246-247), it is well recognised that with regard to standard CV risk factors, patients with renal failure and especially those on RRT are under treated and the prescription of medications such as aspirin, beta-blockers and statins, even after AMI is low(162-163). One could presume that with regard to patients selected for renal transplantation, treatment of CV risk factors and instigation of primary and secondary preventative therapy for CVD should be even more aggressive than that in patients not selected for transplant but whilst there is data available on the baseline demographics, morbidity and mortality of patients listed for renal transplant, there is little information detailing the treatment of CV risk factors and the use of cardioprotective medication in this group of patients.

The aim of this chapter is to describe the baseline demographics of this population of 148 patients with ESRF in the West of Scotland considered suitable for renal transplantation, in addition to assessing the treatment of standard, reversible CV risk factors and the use of cardioprotective medication, both in the primary and secondary prevention of CVD in this population.

3.2 Methods

3.2.1 Subjects and procedure

Patients were recruited from the West of Scotland renal transplant waiting list or from the transplant assessment clinic at the Western Infirmary, Glasgow. All patients gave informed consent and the study had approval from the local ethics committee. The full screening protocol and description of methods used are described in Chapter 2. Patients were recruited between January 2001 and August 2002.

3.2.2 Statistics

Statistical analysis was performed using SPSS Version 11.5 software (SPSS inc. Chicago IL, USA). Baseline data are expressed as mean +/- standard deviation (SD) if normally distributed or median, if not normally distributed. Categorical variables were examined using the Chi-squared test. Differences between two groups were assessed using a two-sample, unpaired t-test (parametric data) or Mann Whitney U test (nonparametric data). A p-value of less than 0.05 was considered significant.

3.3 Results

3.3.1 Age and sex differences

The cohort totalled 148 patients and consisted of 101 men (68%) and 47 women. The age distribution of the cohort is displayed in Graph 3.1. The mean age of the cohort was 50 years with a median of 50 years and age ranged from 24-70 years. One fifth of the cohort (30 patients) was over 60 years of age. Baseline demographics for the whole cohort are shown in Table 3.1.

3.3.2 Aetiology of renal failure

The proportions of patients with different primary causes of renal failure are shown in Figure 3.1. The proportion of patients with glomerulonephritis was 22% and this was the most common individual cause of renal failure in the cohort. Diabetic nephropathy accounted for 17% of ESRF and thereafter adult polycystic kidney disease (11%), chronic pyelonephritis (12%) and nephrosclerosis/hypertensive renal disease (8%) made up smaller proportions. The remaining 30% patients either had an unknown cause of ESRF or the primary cause of ESRF was rare, such as multisystem diseases or pulmonary vascular syndromes.

3.3.3 Length of renal failure and time on renal replacement therapy

As patients in the study were recruited from either the transplant waiting list or from the renal transplant assessment clinic, the ranges for length of renal failure, from point of diagnosis, were large. Times ranged from 2 months to 39 years, with a mean of 99

months and a median of 60 months. The length of time on RRT ranged from 0 months, in those patients assessed for renal transplant at or just prior to inception of RRT, to 12 years in a patient with a previous renal transplant. The mean length of time spent on RRT was 31 months and the median 22 months.

The majority of the cohort (81%) had never undergone previous renal transplantation but 19 patients (13%) had 1 previous failed allograft, 7 patients (4.7%) had 2 previous allografts and 1 patient had previously had 3 transplants.

3.3.4 Type of renal replacement therapy

Similar to other dialysis programmes in the United Kingdom, 60% of the cohort used haemodialysis as mode of RRT and 40% PD. Those using haemodialysis were either attending thrice weekly sessions of 4 hours per session or thrice weekly overnight or 'long time' sessions of 6 hours per session. Patients using PD were either using CAPD or overnight APD. The proportions of each of these 4 modalities are displayed in Figure 3.2. In this cohort of patients, no significant differences were found between those using PD or haemodialysis with regard to CV morbidity, medication taken or renal history. Similarly, there were no significant age or sex differences between those using peritoneal or haemodialysis. For example, the proportion of patients with diabetes using haemodialysis was 17% and using PD 21% ($p= 0.490$) and the proportion of patients with a history of IHD using PD was 23% compared to 18% using haemodialysis ($p= 0.450$).

3.3.5 Standard cardiovascular risk factors

Table 3.1 shows the proportions of patients in the cohort with standard CV risk factors and CV co-morbidity. A relatively low proportion of patients had a history of previous AMI (9.7%) and just under one fifth of the cohort (19.3%) had a history of IHD. A much smaller proportion of patients had a history of CHF (7.6%), and 5.5% of patients had a history of previous cerebrovascular event. Similarly, 5.5% patients had a history of PVD defined as claudication at less than 100 yards or previous documented disease on X-ray angiography or magnetic resonance angiography.

With regard to standard risk factors for IHD, unsurprisingly, the majority of the cohort had a history of hypertension (94.5%). High proportions (36%) also had a history of hyperlipidaemia, defined as those established on statin therapy, 29.2% of patients were current smokers and a further 25% were ex-smokers. Over one quarter of the cohort had a family history of IHD (26.4%) and 18.6% of patients were diabetic.

Diabetic patients had a similar prevalence of IHD (18.5% vs. 19.5%, p=0.908) and previous MI (7.4% vs. 10.2%, p=0.662) than non-diabetic patients and similar proportions of patients in each group had a history of CHF (7.4% vs. 7.6%, p=0.969) (Table 3.2). However, higher proportions of diabetic patients had other forms of vascular disease. A higher but non-significant proportion of diabetic patients had a history of a prior cerebrovascular event (11.1% vs. 4.2%, p=0.160) and diabetic patients were significantly more likely to have a history of PVD (14.8% vs. 3.4%, p=0.019).

With regard to renal history, diabetic patients had spent less time on RRT (20+/-21.3 vs. 34+/-30.2, p=0.007) and had a relatively shorter period of renal failure (45+/-39.1 vs. 112+/-99, p<0.001) than those without diabetes and non-diabetic patients were more

likely to undergo reassessment after a previous failed transplant (22% vs. 3.7%, p=0.026). Only one diabetic patient had undergone prior renal transplantation.

3.3.6 Drug therapy

The proportion of patients prescribed different medications is shown in Table 3.3 and total number of antihypertensives taken by patients is displayed in Figure 3.3. Erythropoietin was the most commonly prescribed drug with 73.6% patients receiving regular erythropoietin therapy. Thereafter, just over one third of the cohort was taking a beta-blocker (36.4%) and 28.7% were taking an ACEI or an angiotensin receptor blocker (ARB). Unsurprisingly, similar proportions of patients were taking aspirin (31.5%) or a statin (31.5%).

With regard to antihypertensive therapy, 33% of the cohort was not prescribed any antihypertensive medication. This is surprising as 95% had a history of hypertension but on the day of screening 49% of patients in the cohort had a normal BP reading. However, 19.4% patients with a hypertensive BP reading (>150/80mmHg) on the day of screening were not taking any antihypertensive medication. Of the remaining 77%, the highest proportion was prescribed one antihypertensive medication and 3% of the total cohort was prescribed 4 antihypertensives.

With regard to other therapy, 12% patients not receiving regular erythropoietin, had haemoglobin concentrations of <11g/dL and a much higher proportion of 49.5% of patients not taking a statin had a total cholesterol of >5.5mmol/L.

3.3.7 Drug therapy in 'high' risk patients

Following the guidelines of the Renal Association (244), 109 of the 148 patients in this cohort should be considered at higher CV risk and undergo formal stress testing and echocardiography for CVD prior to listing for transplantation. It follows that this group of patients should therefore be considered for primary prevention of CVD and prescription of statins and aspirin. This group of patients also includes the subgroups of patients with diabetes, a history of IHD and those who have previously sustained an AMI. Medication prescription for these subgroups of patients is shown in Table 3.4.

A higher proportion of patients in the 'high' risk group were taking cardiac medication compared to the cohort as a whole but overall, the prescription of cardiac medication was still relatively low. The prescription of ACEI or ARB and beta-blockers in diabetic patients was particularly low at 36% and 32% respectively, and apart from the prescription of aspirin, there was a low proportion of patients on secondary prevention after a previous AMI. Only 57.4% of the group of patients who had a previous AMI were taking a statin or were on an ACEI or ARB.

3.3.7 Prevalence of reversible risk factors in 'high' risk patients

The proportions of patients with an elevated BP on the day of screening (>150/80mmHg), a total cholesterol of >5.0mmol/L and a current smoking practice are shown in Table 3.5. The prevalence of all three potentially reversible risk factors was high in patients considered at high CV risk. Even in patients with an established history of IHD and previous AMI, the proportion with a high total cholesterol was over 50% and over 40% of these patients had a hypertensive BP reading on the day of screening.

3.4 Discussion

Advancing age and co-morbidity are well recognised factors influencing selection of patients with ESRF for renal transplantation (10-11). Oniscu *et al.* (11) reported on access to the transplant waiting list for 4523 patients in Scotland starting RRT between 1989 and 1999. The study found that older patients and diabetics were much less likely to be listed for renal transplant. Patients over 60 years old were 80% less likely to be listed compared to patients aged between 18 and 34 and diabetics were 50% less likely to be listed than non-diabetics. Similar results have been observed in American studies but the proportion of diabetic patients both starting RRT and undergoing transplantation in America is higher than that in the UK (13-14). Similarly in this cohort, the proportion of patients over 60 years of age was much lower than that previously reported for patients starting RRT in Scotland. In the study of Oniscu *et al.* 42% of patients commencing RRT were older than 65 and in the later study of Metcalfe *et al.* (27) the proportion of patients over 65 starting RRT was even higher at 48.5%. However, the proportion of older patients being listed for transplant in Scotland does seem to be increasing. Between 1989 and 1999, 10% of the patients listed for transplant in Scotland were over 60 whereas in our cohort, recruited between 2001 and 2002, 20% of patients were over 60.

It is well documented that diabetic patients with ESRF have both a higher CV risk profile and higher CV morbidity compared to those without diabetes (63-64). It is therefore unsurprising that a low proportion of diabetic patients are listed for transplant. Whereas around 24% of patients commencing RRT in Scotland are diabetic, we found that diabetic patients account for only 18% of those on the waiting list. However, this again is a slightly higher proportion than that of previous studies suggesting that higher risk patients

may now be gaining access to transplantation in Scotland. Despite this finding, patients with diabetes in this cohort actually had a slightly lower prevalence of both IHD and MI compared to those without diabetes suggesting that there is still a significant selection bias but suitable diabetic patients seem to be identified earlier in the course of renal failure and once selected, may be listed sooner.

Patients on haemodialysis have a higher level of co morbidity compared to those on PD (32), and older patients with a history of IHD or CHF are more likely to be placed on haemodialysis programmes. In this cohort there was no difference in any aspect of past renal or CV history between those on haemodialysis or PD. This may reflect the long time overnight dialysis programme in the West of Scotland which tends to be attractive to younger fitter patients with ESRF who still work or may reflect a selection bias for fitter patients on haemodialysis to be selected for transplant.

The majority of guidelines regarding the management of CVD in patients with ESRF advise that patients should be regarded to be at high CV risk and that standard CV risk factors should be treated according to guidelines for the general population. However, the underpresciption of cardiac medications such as beta-blockers and statins in patients with ESRF is well recognised. There are several explanations for this phenomenon of 'therapeutic nihilism' including a lack of evidence of the benefits of cardioprotective medication in patients with ESRF due to under representation of such patients in interventional randomised controlled CV trials and concerns regarding drug safety. Since this study was conducted, two other studies have been published detailing the use of cardiac medication in patients awaiting transplant. In 2005 Gill *et al.* (13) reported an extremely low prescription of beta-blockers (30%), ACEI (35%) and statins (28%) in 604

patients listed for transplant in Canada. Sharma *et al.* (33) reported a slightly higher prescription rate in 203 patients listed in London and the proportion of patients taking cardioprotective medication ranged from 35.2% prescribed a beta-blocker to 56.8% prescribed a statin. In our cohort of patients the percentage of patients taking cardioprotective medication was slightly higher than that of the Canadian study but prescription rates were much lower than that of the UK study, apart from beta-blocker prescription which was similar in the two groups. When the cohort was split into higher risk subgroups, the prescription rate increased but alarmingly, less than half of patients with a documented history of IHD were taking aspirin and only one-third of diabetics were prescribed an ACEI or ARB.

The treatment of reversible risk factors was also low. We found that 20% patients who were hypertensive on day of screening were not prescribed any medication to control BP and 50% patients not prescribed a statin had an elevated cholesterol concentration, in what should be regarded as a high risk population. Patients regarded to be at higher CV risk had a high observed prevalence of hyperlipidaemia and hypertension (Table 3.5) and around one fifth were current smokers, including those with a previous AMI. It should be noted however, that BP in this study was a single measurement and 24 hour monitoring may have given a more accurate assessment of mean BP. However, screening was carried out on a post-dialysis day so patients should have been relatively euvolemic.

A major concern with regard to the prescription of drugs such as aspirin and statins in patients with ESRF has been safety, especially the risk of rhabdomyolosis caused by statins and worsening of anaemia in those taking aspirin. Recently the UK-HARP study (248) reported on the safety of the use of simvastatin and aspirin in patients with CRF

including a proportion on RRT and found that both were safe to use in this population of patients. Patients with ESRF have also been shown to benefit from secondary preventative medication after AMI (163,167,170) and carvedilol has been shown to confer mortality benefits in patients on RRT with LVSD (249). However, evidence of mortality benefit as a result of primary prevention of CVD with drugs such as aspirin and statins in this population is still lacking.

Another reason for the underprescription of anti-hypertensive medication in patients on RRT, especially haemodialysis, are the problems of hypotension during dialysis and of hyperkalaemia in patients prescribed ACEI or ARB's. With regard to the former problem, it should be remembered that any form of haemodynamic instability should raise suspicion of underlying cardiomyopathy or CAD and prompt further cardiac investigation as these patients may be the ones to benefit most from cardioprotective medication but hyperkalaemia does limit the use of ACEI in some patients.

Patients in this cohort have many similar characteristics to those of previous studies, both in Scotland and the UK but the proportion of older patients and diabetics gaining access to the waiting list may be increasing in Scotland. Patients listed for transplant have a high prevalence of untreated, potentially reversible standard CV risk factors. The use of cardioprotective medication is low in this population, even in high risk groups and an obvious initial strategy to improve CV morbidity and mortality in this population would be to aggressively control reversible risk factors and to increase the prescribing practice of cardioprotective medication as per current guidelines. Strategies such as specific cardiac risk or cardio-renal clinics for patients with CRF may offer a way of achieving this.

Graph 3.1 Age distribution of 148 patients with ESRF felt suitable for renal transplantation

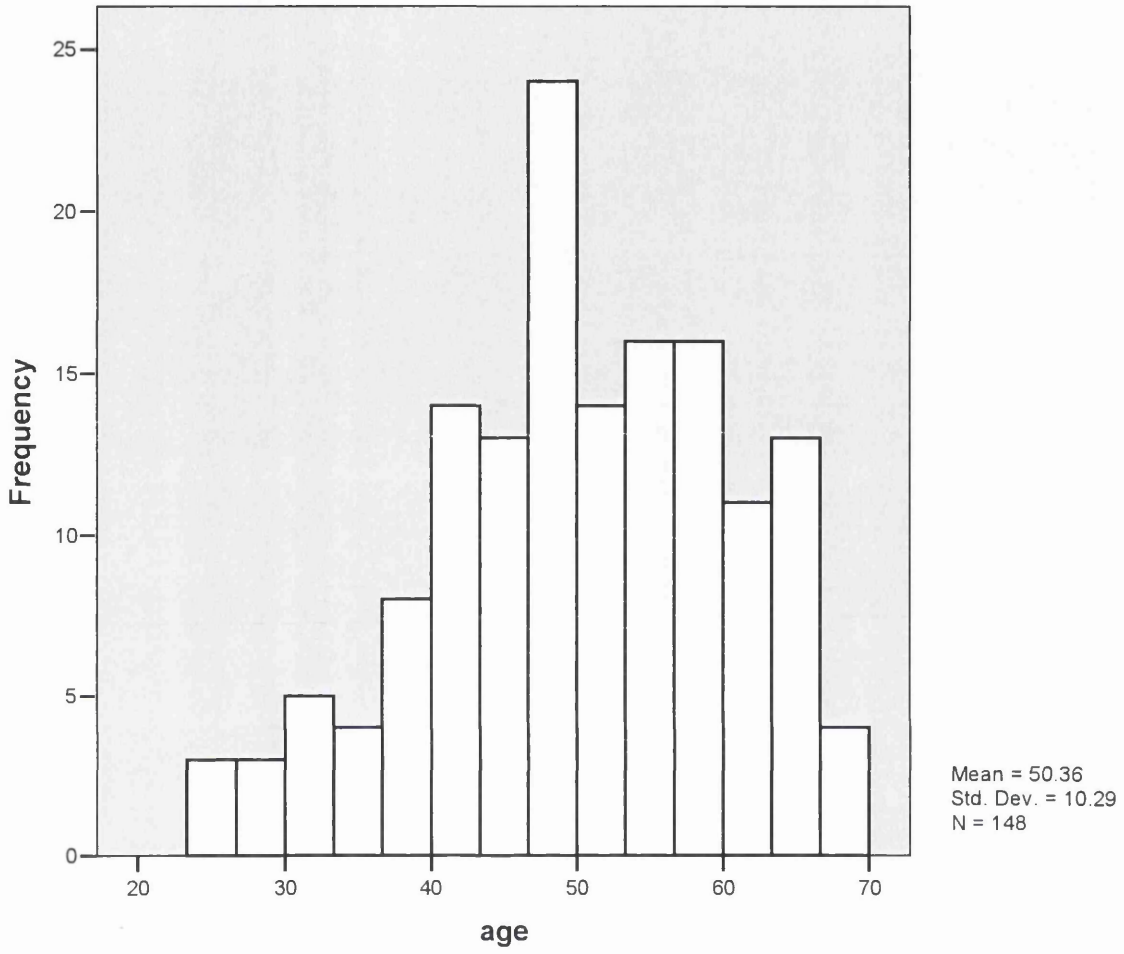


Table 3.1 Baseline demographics in a cohort of 148 patients with ESRF felt suitable for renal transplantation

Baseline Variable	
Age (years +/-SD)	50 +/-10
Sex (%male)	68.2
Patients using haemodialysis (%)	60
Length of time on RRT (months/range)	31.6 (0-144)
Length of renal failure (years/range)	8.2 (0.2-39)
Previous renal transplant (%)	18.2
History of Ischaemic Heart Disease (%)	19.3
Previous myocardial infarction (%)	9.7
History of chronic heart failure (%)	7.6
Diabetic (%)	18.6
History of hypertension (%)	94.5
History of hyperlipidaemia (%)	36
Current smoker (%)	29.2
Family history of IHD (%)	26.4
Cerebrovascular disease (%)	5.5
Peripheral vascular disease (%)	5.5
Systolic blood pressure (mmHg+/-SD)	136+/-24
Diastolic blood pressure (mmHg+/-SD)	80+/-12
Cholesterol level (mmol/L+/-SD)	5.6+/-1.7
Haemoglobin (g/dL+/-SD)	11.5+/-1.6

Figure 3.1 Primary causes of renal failure

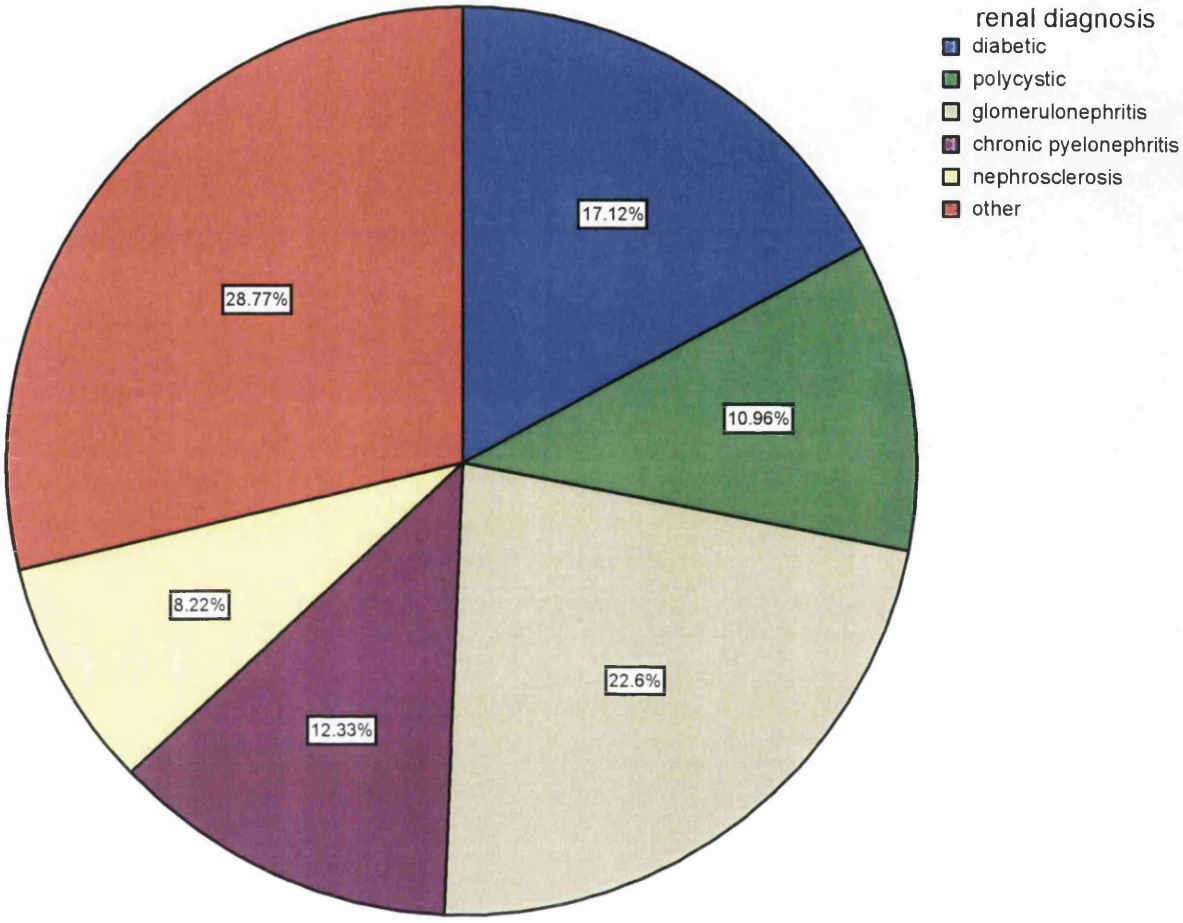


Figure 3.2 Types of dialysis therapy

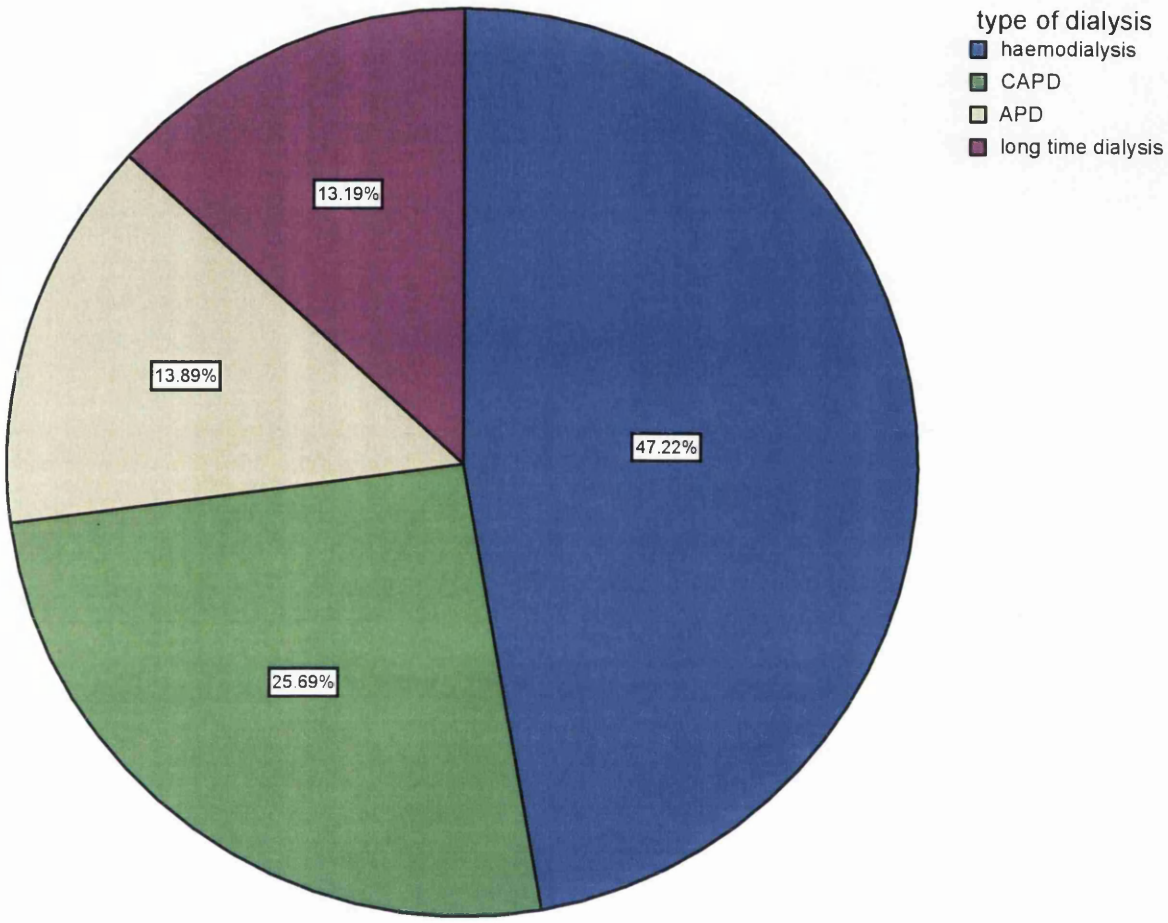


Table 3.2 Differences between diabetic and non-diabetic patient baseline demographics and standard CV risk factor profile

Variable	*Diabetic n=25*	*Non-diabetic n=123*	*p-value*
Age (years)	48+/-10.9	50+/-10.1	p=0.395
Sex (% male)	77.8	65.3	p=0.211
Length of renal failure (months)	45+/-39.1	112+/-99	p<0.001*
Time on RRT (months)	20+/-21.3	34+/-30.2	p=0.007*
Type of RRT (% using HD)	53.8	61.2	p=0.490
Previous transplant (%)	3.7	22.0	p=0.026*
Previous MI (%)	7.4	10.2	p=0.662
Ischaemic heart disease (%)	18.5	19.5	p=0.908
Chronic heart failure (%)	7.4	7.6	p=0.969
Cerebrovascular disease (%)	11.1	4.2	p=0.160
Peripheral vascular disease (%)	14.8	3.4	p=0.019*
Hypertension (%)	100	93.2	p=0.165
Hyperlipidaemia (%)	48.1	33.1	p=0.141
Family history of IHD (%)	14.8	29.1	p=0.131
Current smoker (%)	22.2	30.8	p=0.194

Table 3.3 Prescribed medication for total cohort

Medication	*Proportion of patients (%)*
Erythropoietin	73.6
Aspirin	31.5
Beta-blocker	36.4
ACEI or ARB	28.7
Calcium channel blocker	21.0
Doxasosin	11.2
Nitrate	7.7
Diuretic	32.2
Statin	31.5

Figure 3.3 Number of antihypertensive medications prescribed per patient

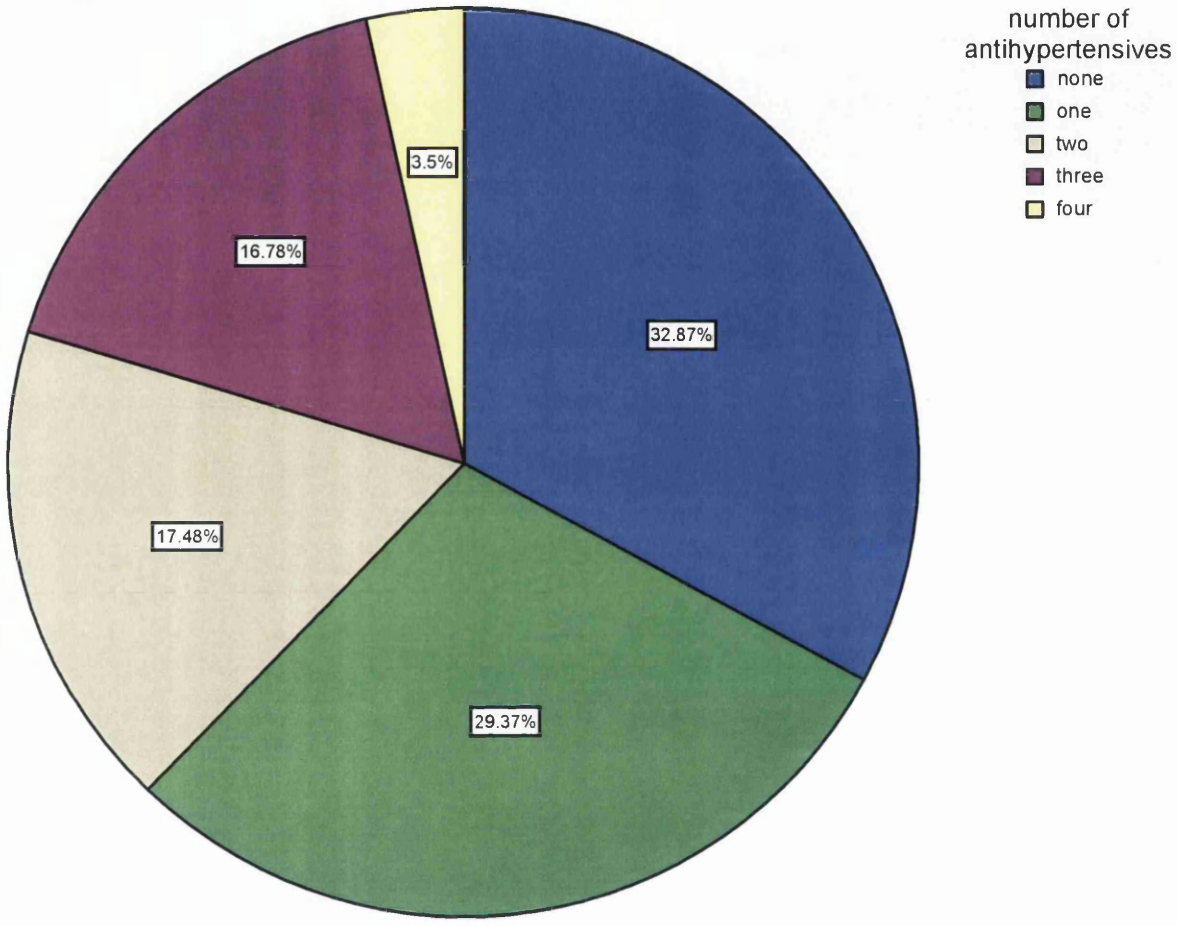


Table 3.4 Cardioprotective medication prescription in high CV risk subgroups

Drug	***All 'high' risk patients n=109***	***Diabetes n=25***	***IHD n=29***	***AMI n=15***
Aspirin	42.3%	52%	42.9%	85.7%
Beta-blocker	40.4%	32%	71.4%	64.3%
ACEI/ARB	33.6%	36%	53%	57.1%
Statin	39.4%	52%	60.7%	57.1%

Table 3.5 Prevalence of potentially reversible standard CV risk factors in high risk subgroups

Risk Factor	***All 'high' risk patients n=109***	***Diabetes n=25***	***IHD n=29***	***AMI n=15***
Hypertension	52.3%	55.6%	42.9%	42.9%
High chol	62.9%	59.1%	56.0%	58.3%
smoker	31.4%	22.2%	25.9%	21.4%

Chapter 4

Prevalence, Pattern and Determinants of Left Ventricular Abnormalities

4.1 Introduction

The finding of an abnormal LV in a patient with ESRF confers an adverse prognosis for that patient compared to a patient with ESRF and a normal LV (37,71). Furthermore, such a finding also implies that patient is more likely to develop IHD or CHF (29,30,37). The pattern of the LV abnormalities identified will provide information regarding how soon the patient can expect to develop symptoms of CHF or IHD and how long they are likely to survive (17,71). High systolic BP has been most consistently associated with the most common LV abnormality, concentric LVH, whereas IHD is more often associated with the LV abnormality that confers the poorest outcome, LVSD (29,30,47,71,76). Other potential risk factors for LV abnormalities include older age, diabetes and anaemia. However, what is not established is whether consistent improvement or regression of such ventricular abnormalities is possible in this population and whether regression will result in an improved outcome for the patient. In other words, although we know that the patient sitting in front of us at the clinic with LVH and LVSD will have a poor outcome we don't know if we can improve that outcome. Furthermore, as LV abnormalities are so prevalent in this population we therefore do not know if we can improve the outcome of up to 85% of patients with ESRF (69).

This is not the case for the general population, where large adequately powered interventional trials have shown that regression of LVH and improvement of LVEF is

possible by targeting BP with antihypertensive medication in the case of the former and the use of ACEI and beta-blocker therapy in the latter. Both strategies result in improvements in outcome (250-252).

Although echocardiography is, and will remain, an invaluable tool for the assessment of cardiac structure and function there has been a move away from its use in studies targeting LV mass or function because of the large ranges of variability of measurement associated with the technique (183). This means large sample sizes are required and whilst previous studies in the normal population recruited several thousand patients, the largest interventional study targeting LVH in patients with ESRF to date involved only 150 patients (75). Echocardiography poses additional problems in patients with ESRF and previous studies have suggested that echocardiography overestimates LV mass compared to CMR imaging (202). As CMR is a more direct method of measuring LV mass and volumes, with a much higher spatial resolution compared to echocardiography, the range of variability is much smaller and a reduction of sample size of over 90% can be expected when using CMR imaging as opposed to echocardiography in either longitudinal or interventional studies targeting LV function (213).

We therefore aimed to assess the utility of CMR imaging in patients with ESRF awaiting transplant and to measure the prevalence and pattern of LV abnormalities using a method of measurement which is not dependant on EDV for the calculation of LV mass. We also aimed to identify the determinants of LV abnormalities defined by CMR in order to design future interventional trials to investigate whether regression of LV abnormalities is possible and if so, whether it confers improved outcome for patients with ESRF.

4.2 Methods

4.2.1 Subjects

Patients were recruited from the West of Scotland renal transplant waiting list or from the transplant assessment clinic at the Western Infirmary, Glasgow. All patients gave informed consent and the study had approval from the local ethics committee. The full screening protocol and description of methods used are described in Chapter 2.

4.2.2 Procedure

148 patients attended for an initial screening visit as described in Chapter 2. Measured LV volumes and mass were corrected for BSA. The normal ranges for LV parameters in males and females are shown in Table 4.1(253).

4.2.3 Statistics

Statistical analysis was performed using SPSS Version 11.5 software (SPSS inc. Chicago IL, USA). Baseline data are expressed as mean +/- SD or median, if not normally distributed. Differences between the groups were assessed using a two-sample t test (normally distributed data) or Mann Whitney U test (non-parametric data). A p-value of less than 0.05 was considered significant. 95% confidence intervals for differences between groups in mean percentage change from baseline are given. Correlations between continuous values were assessed using Pearson's correlation coefficient for parametric data. The determinants of LV abnormalities were identified using multivariate linear regression analysis using a stepwise paradigm.

4.3 Results

4.3.1 Baseline Characteristics

Data was available for 148 patients for the initial analysis on prevalence of LV abnormalities. Baseline demographics, including CV risk factors, for the whole cohort are discussed in Chapter 3 and shown in Table 3.1. Average systolic BP for the cohort was 136+/-24mmHg and average diastolic BP was 80+/-12mmHg. Average haemoglobin level was relatively high for a group of patients with ESRF at 11.5+/-1.6g/dL.

4.3.2 Baseline left ventricular anatomy and function and prevalence of left ventricular abnormalities

Baseline measurements for LV function, mass and volumes are found in Table 4.2 with the corresponding normal ranges for men and women using CMR imaging (253). In the baseline cohort of 148 patients, 29% had a normal LV as defined by CMR imaging. In keeping with previous studies the most common LV abnormality was elevated LV mass with a total of 70% of patients being identified with LVH. LVDil was found in 17% of patients and 15% had LVSD. Unsurprisingly, a particular patient could have more than one LV abnormality and 11% of the cohort (16 patients) had a combination of all three LV abnormalities. The relationship of these LV abnormalities to each other is shown in Figure 4.1. LVH was ubiquitous in those with LV abnormalities and only 1 patient with an abnormal LV did not have LVH. LVDil did not occur in isolation and was always associated with LVH with or without LVSD. Similarly, LVSD was usually observed in association with LVH and LVDil with a small number associated only with LVH.

Categorising the LV abnormalities observed into the previously described patterns of cardiomyopathy in patients with ESRF, 50% of patients had concentric LVH, 6% had eccentric LVH and 15% had LVSD (Figure 4.2). Thus the pattern of differing types of cardiomyopathy in this cohort measured using CMR is different to that previously described by other groups using echocardiography (Figure 1.1).

4.3.3 Baseline correlates of left ventricular anatomy and function

The relationship between systolic BP and the baseline LV abnormalities is demonstrated in Graphs 4.1-4.4. Systolic and diastolic BP correlated well with LV mass ($p<0.001$, $r=0.410$), ($p=0.001$, $r=0.412$) and EDV ($p<0.001$, $r=0.374$), ($p=0.009$, $r=0.215$) but not with ESV ($p=0.023$, $r=0.201$) ($p=0.187$, $r=0.117$) and neither correlated significantly with Ejection Fraction ($p=0.586$), ($p=0.687$). There was no correlation with any baseline LV abnormality and age but there was a significant correlation between sex and LVMI and a weak but significant negative correlation between heart rate and Ejection Fraction ($p=0.003$, $r=0.283$).

4.3.4 Characteristics of patients with left ventricular abnormalities

The differences between patients who had normal left ventricles (control group) defined by CMR and those who had abnormal ventricles are shown in Table 4.3 and the differences found in LV measurements in Table 4.4. There was no significant difference between the groups with regard to age or sex. With regard to history of renal disease, there was no difference between the groups with regard to length of CRF ($p=0.333$), length of time on RRT ($p=0.807$) or number of previous transplants ($p=0.914$). There was

however, a significant difference between those with a normal ventricle and an abnormal ventricle and mode of RRT. Patients who had an abnormal LV were more likely to be on haemodialysis (61%) compared to those with a normal ventricle (45%) p=0.038.

With regard to standard CV risk factors there were significant differences between the groups with regard to both systolic and diastolic BP. Patients with an abnormal LV were more likely to have both a higher systolic BP (141.0+/-22.7mmHg vs. 124.3+/-24.3mmHg, p<0.001) and diastolic BP (82.5+/-11.5mmHg vs. 74.0+/-11.2mmHg, p<0.001) than those with a normal LV. Similar to findings in previous echocardiographic studies there were no significant differences between the groups with regard to other standard CV risk factors. Patients with an abnormal LV were no more likely to have a past history of IHD (p=0.959), diabetes (p=0.073) or a past history of other vascular disease (p=0.064). There were no significant differences between the groups with regard to a history of hypertension, smoking or family history of IHD.

Interestingly, despite the differences in BP between the two groups, there were no significant differences between those with a normal LV and an abnormal LV with regard to type of antihypertensive medication (Table 4.5) such as beta-blockers (p=0.104) or ACE inhibitors (p=0.292), number of prescribed antihypertensive drugs (p=0.063) or the use of aspirin (p=0.205) or statins (p=0.482).

Finally, turning to biochemical markers there were no differences between the groups with regard to haemoglobin (p=0.214), CRP (p=0.254) or cholesterol level (p=0.066) but the patients with an abnormal ventricle had significantly higher levels of BNP (p<0.001).

4.3.5 Characteristics of patients with isolated left ventricular hypertrophy

Turning to the individual LV abnormalities, each group of abnormalities were compared to the patients in the cohort with a 'normal' LV to ascertain any potential differences between patients with findings of isolated LVH, LVDil and LVSD and are shown in Table 4.3.

LVH was the most common LV abnormality in the cohort and 70% patients were found to have this abnormality. Of those patients with an abnormal LV, 68% of these had isolated LVH (50% of total cohort) and this group was compared to those patients with a normal LV. With regard to baseline characteristics there were no age or sex differences between the groups and no significant differences were seen with regard to total length of renal failure or length of time on RRT. The only significant difference with regard to renal history between the groups was type of RRT, and 65.7% patients with concentric LVH were established on haemodialysis compared to 45% patients with normal left ventricles (p=0.047).

Patients with concentric LVH had a significantly higher systolic (140.7+/-23.6mmHg vs. 124.3+/-24.3mmHg, p=0.001) and diastolic (82.8+/-11.9mmHg vs. 74.0+/-11.2mmHg, p<0.001) BP than those in the control group and similar to the initial analysis of all patients with an abnormal LV there were no significant differences between the groups with regard to previous history of IHD (p=0.241), diabetes (p=0.383) or other vascular disease (p=0.122). Patients with concentric LVH were no more likely to be on a beta-blocker (p=0.154) or ACE inhibitor (p=0.870) and were not taking a higher number of antihypertensive medications (p=0.203) than those with normal ventricles, although the

proportions on these medications in the group with concentric LVH was higher (Table 4.5).

Finally, there were no significant differences with regard to haemoglobin level (11.6+/-1.5g/dL vs. 11.9+/-1.6g/dL, p=0.489) or cholesterol level (5.7+/-1.6mmol/L vs. 6.0+/-1.7mmol/L) but lgBNP was significantly higher in those with concentric LVH (2.9 vs. 1.4, p<0.001).

4.3.6 Characteristics of patients with left ventricular dilation

A total of 17% patients in the cohort had LVDil defined by CMR imaging. It should be noted that patients who had LVDil consisted of a small number categorised as eccentric LVH (9 patients) and the rest had associated LVSD which may confound results for this group. There were no differences with regard to sex and age between patients with LVDil and those with normal ventricles but once again there were significant differences in BP between the two groups. (Table 4.3). Systolic BP was significantly higher in the patients with LVDil (144.3+/-19.9mmHg vs. 124.3+/-24.3mmHg, p=0.011) as was diastolic BP (87.0+/-8.2mmHg vs. 74.0+/-11.2mmHg, p<0.001) when compared to patients with normal ventricles.

In contrast to the findings in the group analysis of all those with LV abnormalities and that of patients with LVH, patients with LVDil were no more likely to be on haemodialysis than those with a normal ventricle (p=0.443). With regard to vascular disease and diabetes, patients with LVDil did not have a significantly higher prevalence of IHD (p=0.553) or diabetes (p=0.965), than those with normal ventricles but did have a

significantly higher prevalence of other vascular disease ($p<0.001$) and a significantly higher proportion of those with LVDil had a previous history of CHF ($p=0.006$)

Turning to medication, the use of ACE inhibitors was significantly higher in patients with LVDil ($p=0.044$) as was use of calcium channel blockers ($p=0.044$). There were no other significant differences between the two groups with regard to medication type or number of antihypertensive medications taken (Table 4.5).

As expected, patients with LVDil had similar haemoglobin levels to those with normal ventricles (11.2g/dL vs. 11.9g/dL, $p=0.284$) and the only biochemical abnormality that was significantly different between the two groups was BNP with a significantly higher lgBNP observed in the patients with dilated ventricles (3.2 vs. 1.4, $p=0.016$).

4.3.7 Characteristics of patients with left ventricular systolic dysfunction

Although only 7.6% patients had a documented history of LVSD prior to screening, 15% patients had LVSD as defined by CMR. This group also includes all patients with a combination of all three LV abnormalities as 70% patients with LVSD also had associated LVH and LVDil.

Although there were no significant differences with regard to age between patients who had LVSD and those in the control group, this was the only group patients with LV abnormalities to have a significant difference in sex and 87% of those with LVSD were male ($p=0.015$). In contrast to the other groups of patients with LV abnormalities there were much smaller differences between those with LVSD and those with normal ventricles with regard to BP. Systolic BP was significantly higher in those with LVSD (136.9mmHg+/-22.2mmHg vs. 124.3+/-24.3mmHg, $p=0.043$) but there was no

significant difference with regard to diastolic BP (78.7+/-10.6mmHg vs. 74.0+/-11.2mmHg, p=0.104) and no significant differences in any aspect of renal history, including type of dialysis therapy.

What was significantly different however, was a previous history of AMI (p=0.010), IHD (p=0.027), other vascular disease (p=0.005) and CHF (p=0.009). A prior history of any of these conditions was significantly more likely in the group of patients with LVSD, as was a history of diabetes (p<0.001) (Table 4.3). In view of this it is unsurprising that patients with LVSD were more likely to be taking aspirin (p<0.001) and ACE inhibitors (p<0.010) but they were not more likely to be taking a beta-blocker (p=0.184) or a statin than those patients with a normal LV (p=0.854) (Table 4.5).

With regard to haematological and biochemical markers there was no difference in haemoglobin level between those with LVSD and those with a normal LV (11.2+/-1.5mmol/dL vs. 11.8+/-1.6mmol/dL, p=0.127) but lgBNP was significantly higher (4.5 vs. 1.4, p<0.001) and cholesterol levels were significantly lower in patients with LVSD (4.7+/-1.6 vs. 6.0+/-1.6mmol/L, p<0.001).

4.3.8 Relationship between left ventricular abnormalities and the ECG

Differences in ECG findings between the groups are displayed in Table 4.6 Patients with LV abnormalities were more likely to have an abnormal ECG with regard to criteria of LVH (14.3% vs. 47%, p=0.001), ST changes (7.1% vs. 37%, p=0.001) and the presence of Q waves (2.4% vs. 6.8%, p=0.025) and patients with history of IHD and prior AMI were more likely to have Q-waves on their ECG (p<0.001).

However, the sensitivity of the ECG to detect abnormalities of LV anatomy and function was generally unsatisfactory with a sensitivity of 39.0% and a specificity of 81.0%. The NPV of the ECG to exclude those with LV abnormalities was also poor at 65% with a PPV of 83%.

4.3.9 The determinants of left ventricular abnormalities defined by CMR

Finally, the determinants of LV abnormalities were identified using multivariate linear regression analysis and results are displayed in Table 4.7. The continuous variables of LVMI, EDV corrected to BSA, ESV corrected to BSA and LVEF were tested as outcome variables for the whole cohort. A set of independent variables consisting of age, sex, systolic and diastolic BP, a history of IHD, diabetes or CHF, length of renal failure, type of dialysis therapy and haemoglobin were examined as potential determinants in a backward elimination strategy.

Significant independent determinants of LV mass were sex ($p=0.002$), diastolic BP ($p<0.001$), haemodialysis as mode of RRT ($p=0.014$) and a history of diabetes ($p=0.004$). A history of IHD was not an independent determinant of LV mass.

Similarly to LV mass, diastolic BP ($p<0.001$) and haemodialysis as mode of RRT ($p=0.019$) were independent predictors of EDV and a history of CHF was also a predictor of EDV ($p=0.003$). However, BP and mode of RRT were not predictors of ESV, whereas a history of IHD ($p=0.030$), CHF ($p=0.037$) and diabetes ($p=0.007$) were predictors of ESV. Finally, Ejection Fraction was not dependant on any measure of BP but was dependant on a history of prior IHD ($p=0.022$) or CHF ($p=0.006$) and a history of diabetes ($p=0.001$).

When BNP was included in the regression model it was found to be an independent predictor of all parameters of LV mass, volumes and function measured and was found to be most strongly associated with LV mass.

4.3.10 The concept of LV concentric remodelling

In the original LV geometry trials in hypertensive patients, a fourth pattern of LV geometry was identified in addition to normal geometry, concentric LVH and eccentric LVH; that of concentric remodelling (Figure 4.3). This is described as normal LV mass and increased relative wall thickness of the LV resulting in a small cavity LV and has not been included in previous echocardiographic classification of uraemic cardiomyopathy. Using the definition criteria for concentric remodelling, a further 17 patients (10 men) or 11.5% of the cohort would be categorised in this group from the normal LV group leaving only 17.5% of the total cohort with a normal LV.

This group interestingly, had a significantly lower mean BP than that in either patients with a normal LV or the rest of the cohort taken as a whole. Mean BP for patients with concentric remodelling was 112+/-20mmHg and 71+/-13mmHg for systolic and diastolic BP respectively. Patients who had a normal LV had a significantly higher systolic BP (132+/-23mmHg, $p=0.006$) but diastolic BP was not significantly different.

Both systolic BP and diastolic BP were significantly lower in patients in the concentric remodelling group when compared to the rest of the cohort who had a systolic BP of 139+/-23mmHg, $p<0.001$) and diastolic BP of 81+/-11mmHg, $p=0.001$)

The significance if any, in this patient group of concentric remodelling is unknown and has not previously been investigated. In view of this we elected to simply describe the

pattern of concentric remodelling, rather than include it in the main analysis, as it would introduce a further confounding effect and used the previously defined types of uraemic cardiomyopathy from earlier echocardiographic studies in patients with ESRF.

4.4 Discussion

Previous echocardiographic studies have established that LV abnormalities such as LVH, LVDil and LVSD are common in patients with ESRF and are associated with a poor outcome (14,16-17,29,42,69,74). In this study of 148 patients with ESRF suitable for renal transplantation, 29% were found to have a normal LV as defined by CMR imaging. This is almost twice that found in previous echocardiographic studies of patients with ESRF (69,72-73) and may reflect the fact that patients assessed for renal transplant have less co-morbidity than the unselected groups of dialysis patients in previous studies. For example, this cohort of patients included a relatively low proportion of diabetics at 18% whereas in the study of Parfrey *et al.* (69), the proportion of diabetics was higher at 27% However, in contrast to the higher prevalence of normal ventricles, similar proportions of patients were found to have LVSD in our study, compared to the studies of Parfrey *et al.* at 15%. The pattern of LV abnormalities was also different. Concentric LVH was the predominant LV abnormality but unlike previous studies we found a lower total prevalence of LVDil (16%) and a higher proportion of those who had LVDil, had this in association with LVSD (Figure 4.1). Only 6% of the cohort were found to have eccentric LVH. Thus, whilst a fitter population of patients may explain why fewer have an abnormal LV compared to echocardiographic studies of unselected haemodialysis patients, it does not explain the difference in the pattern of LV abnormalities found.

Ganau *et al.* (254) described 4 different patterns of LV geometry in patients with essential hypertension; normal, concentric LVH, eccentric LVH and concentric remodelling (Figure 4.2). Although we are familiar with the first 3 patterns the fourth pattern is not often described as total LV mass is normal. However relative wall thickness

is increased due to a decrease in LV cavity size. This pattern of LV geometry is felt to reflect remodelling from concentric LVH or a pattern of geometry that develops in response to pressure overload in some patients and the mortality rate in patients displaying this type of geometric pattern is lower than that of eccentric and concentric LVH but higher than that of normal geometry. Concentric remodelling may imply additional problems in patients on haemodialysis as CO is decreased and chamber size is small and therefore this group of patients may be particularly sensitive to abrupt changes in preload during dialysis and be at high risk of dialysis induced hypotension (255).

When considering together the prevalence of concentric LVH and concentric remodelling it is felt that pressure overload is the fundamental abnormality in patients with arterial hypertension although in most circumstances it is associated with some volume component. In hypertensive patients without CAD, regression of concentric LVH to eccentric LVH confers a favourable prognosis (256). However, in cross sectional studies, hypertensive patients with eccentric LV geometry are more likely to have underlying CAD than patients with concentric LVH (257). Thus the natural history seems to be a high prevalence of concentric LVH during the natural progression of arterial hypertension toward overt CVD and a higher prevalence of eccentric LVH once CVD has occurred, as a consequence of post infarction remodelling which will lead to systolic dysfunction.

Although volume overload will be more predominant in patients with CRF compared to those with essential hypertension, the pattern of abnormalities found in our study fit well with the pattern observed in patients with essential hypertension. The predominant LV abnormality found was concentric LVH (50% of whole cohort), which was associated

with BP and a much smaller proportion had eccentric LVH (6% of whole cohort). A dilated LV was more likely to be observed in association with LVSD (10.1%) and this group were observed to have a higher prevalence of IHD and diabetes. This is in contrast to the study of Parfrey *et al.* where 28% of patients were classified as having eccentric LVH.

The higher prevalence of eccentric LVH in echocardiographic studies in patients with ESRF may reflect differences in the technique used to measure the LV, namely echocardiography and CMR. The difficulty in classifying LVH into either a concentric or eccentric type in haemodialysis patients is well recognised when using echocardiography because of cyclical variations in extracellular fluid volume (194-195). The internal dimensions of the LV are influenced by volume status and therefore LV diameter will be different at any given time point in relation to dialysis cycle (194-195). This induces 'acute' changes in relative LV wall thickness and the same patient could be characterised to having either eccentric or concentric hypertrophy depending on the time point of echocardiography. It should be noted that this is a younger, more motivated population, more likely to adhere to fluid restriction and our group as a whole had higher haemoglobin levels than other studies and so these findings do need to be interpreted with caution in comparison to other cohorts. In the recent echocardiographic study of transplant candidates by Sharma *et al.* 11% of patients were found to have eccentric LVH. This study used more accurate 2-D methods of measurement for LV volumes and harmonic imaging, neither of which were used in earlier studies and therefore the lower proportion of eccentric LVH may reflect either more accurate measurement of true LV volumes and mass or reflect a fitter population (patients with known LVSD were

excluded from this study). However, despite this the proportion of patients with eccentric LVH in the study of Sharma *et al.* was still nearly twice that of our study.

LV abnormalities often overlap and co-exist making analysis of individual abnormalities difficult but the pattern of LV abnormalities observed in this study does not support the generally accepted hypothesis that 'uraemic cardiomyopathy' initially exists as either concentric or eccentric LV hypertrophy (79) but rather LVDil may be an intermediate disease stage between LVH and LVSD as observed in the hypertensive population as we did not observe LVDil in isolation. This hypothesis is partly supported by the recent study of Aoki *et al.*(258) They studied the pathological ventricular characteristics of 40 patients on haemodialysis found to have dilated cardiomyopathy and normal coronary arteries. LV biopsies were taken at catheterisation and compared to biopsies in a group of patients with dilated cardiomyopathy and normal coronary arteries who did not have a history of renal failure. On histological examination severe myocyte hypertrophy and disarray was observed in patients on dialysis compared to the control group and the pattern observed in the dialysis group was typical of that associated with the dilated phase of hypertrophic cardiomyopathy.

Despite overlap of LV abnormalities, when groups of patients with each LV abnormality were compared to those with normal ventricles, specific differences were found between groups especially between those with LVH and those with LVSD. Overall, BP correlated well with LV mass and EDV for all patients in the cohort but did not correlate with EF. This was reflected in the finding that both systolic and diastolic BP were significantly higher in the group of patients with elevated LV mass but no such difference were found in the group with LVSD.

The other major difference between the groups was with regard to a history of IHD. Whereas patients with LVSD had a much higher prevalence of IHD than those with normal ventricles, those with LVH did not and the proportion of patients with IHD increased from 11% to 27% to 45% with findings of hypertrophy, dilation and systolic dysfunction.

Thus, in patients with concentric LVH, BP and mode of dialysis therapy determined LV abnormalities when compared to those with normal ventricles, whereas in those with LVSD a history of IHD and diabetes determined LV abnormalities. This finding has been observed in other studies. Foley *et al.* found consistently in studies of their cohort of 433 patients that IHD was associated with LVSD, but not with dilation or hypertrophy (17,69,29) but with follow up, no association between serial echocardiographic changes to LV abnormalities and IHD was found (70).

These findings suggest that although LVH and LVSD are interrelated, the major mechanisms for the development of LVH and LVSD are different. LVH is more dependant on BP and haemodynamic influences such as haemodialysis and LVSD is more dependant on the effects of pre-existing IHD and diabetes. It could therefore be proposed that the two major types of uraemic cardiomyopathy are in fact concentric hypertrophic cardiomyopathy and ICM both of which maybe associated with LV dilation. With regards to targeting risk factors, BP was the only reversible risk factor identified in patients with concentric LVH and LVDil and no traditional reversible risk factors were identified to target in those with LVSD.

Unusually in studies in patients with ESRF, diastolic BP showed a stronger relationship to LVMI in this study. Whereas both systolic and diastolic BP were significantly higher

in patients with LVH, only diastolic BP was independently associated with LVMI and the reasons for this are unclear but may reflect the greater range of variability observed with systolic BP and the fact the only a single measurement of BP was used rather than mean 24 hour values.

Although only 7.6% of patients in the study had a preceding history of heart failure, twice as many were found to have LVSD, a finding which implies worsened prognosis when compared to that of LVH or LVDil (17,70,88). This suggests that either LVSD is under detected prior to patient assessment for renal transplant or is not detected in those who develop LVSD whilst on the waiting list. In either case, if these high risk patients are to be identified prior to undergoing renal transplantation, improved screening for systolic dysfunction is required so that attempts can be made to modify and minimise risk both pre-transplant and in the peri and post-transplant period.

The use of the standard 12 lead ECG to detect LV abnormalities is not a sensitive enough tool to be used in clinical practice in this population. Although an abnormal ECG was a relatively specific sign of LV abnormalities the finding of a normal ECG does not exclude LV abnormalities reliably and therefore other additional non-invasive methods are required to identify LV abnormalities when assessing patients for renal transplantation.

The aim of this study was to determine the prevalence of LV abnormalities of patients with ESRF suitable for renal transplantation using CMR and to identify the determinants of these LV abnormalities. CMR was well tolerated by patients and 71% of patients had an abnormal ventricle which is a smaller proportion than observed in previous echocardiographic studies of transplant candidates. The predominant abnormality was

concentric LVH, found in 50% of the cohort and the proportion of patients with eccentric LVH was very small compared to previous studies. BP and haemodialysis as choice of dialysis therapy were independent predictors of LVH, suggesting a relationship with pressure and volume overload and future interventional studies should target BP control via antihypertensive therapy and manipulation of dialysis programmes in those with concentric LVH.

Patients with LVSD displayed a strong relationship with IHD and diabetes, neither of which are reversible. However, future studies in patients with LVSD and ESRF could assess ischaemic burden, especially the degree of reversible ischaemia which could provide an interventional target in this population of patients with ESRF and poor prognosis.

Further studies are required; both larger studies in patients undergoing assessment for renal transplantation and in unselected patients on RRT using CMR to provide further evidence that ischaemic cardiomyopathy rather than eccentric hypertrophy is the main type of uraemic cardiomyopathy after concentric hypertrophy in patients with ESRF.

Table 4.1 Normal ranges for LV parameters using CMR with SSFP sequence and baseline LV parameters in a cohort of 148 patients with ESRF felt suitable for renal transplantation, defined by CMR

MEN			***ESRF cohort***
PARAMETER	ABSOLUTE	NORMALIZED TO BSA	
LVEDV	168+/-33(102-235)ml	82+/-15(53-112)ml/m^2	82(+/-31)ml/m^2
LVESV	60+/-16(28-92)ml	29+/-7(15-43)ml/m^2	31(+/- 23)ml/m^2
LVSV	107+/-21(65-149)ml	52+/-10(32-72)ml/m^2	49(+/-17)ml/m^2
LVEF	64+/-5(54-74)%		63(+/-12)%
LVM	133+/-24(85-181)g	65+/-9(47-83)g/m^2	114(+/-34)g/m^2
WOMEN			
LVEDV	135+/-19(96-174)ml	77+/-10(57-97)ml/m^2	67(+/-25)ml/m^2
LVESV	49+/-11(27-71)ml	24+/-5(14-34)ml/m^2	22(+/-21)ml/m^2
LVSV	86+/-12(62-110)ml	42+/-6(30-54)ml/m^2	45(+/-13)ml/m^2
LVEF	64+/-5(54-74)%		69(+/-11)%
LVM	90+/-12(66-114)g	52+/-8(36-68)g/m^2	85(+/-27)g/m^2

LVEDV- left ventricular end-diastolic volume

LVESV- left ventricular end-systolic volume

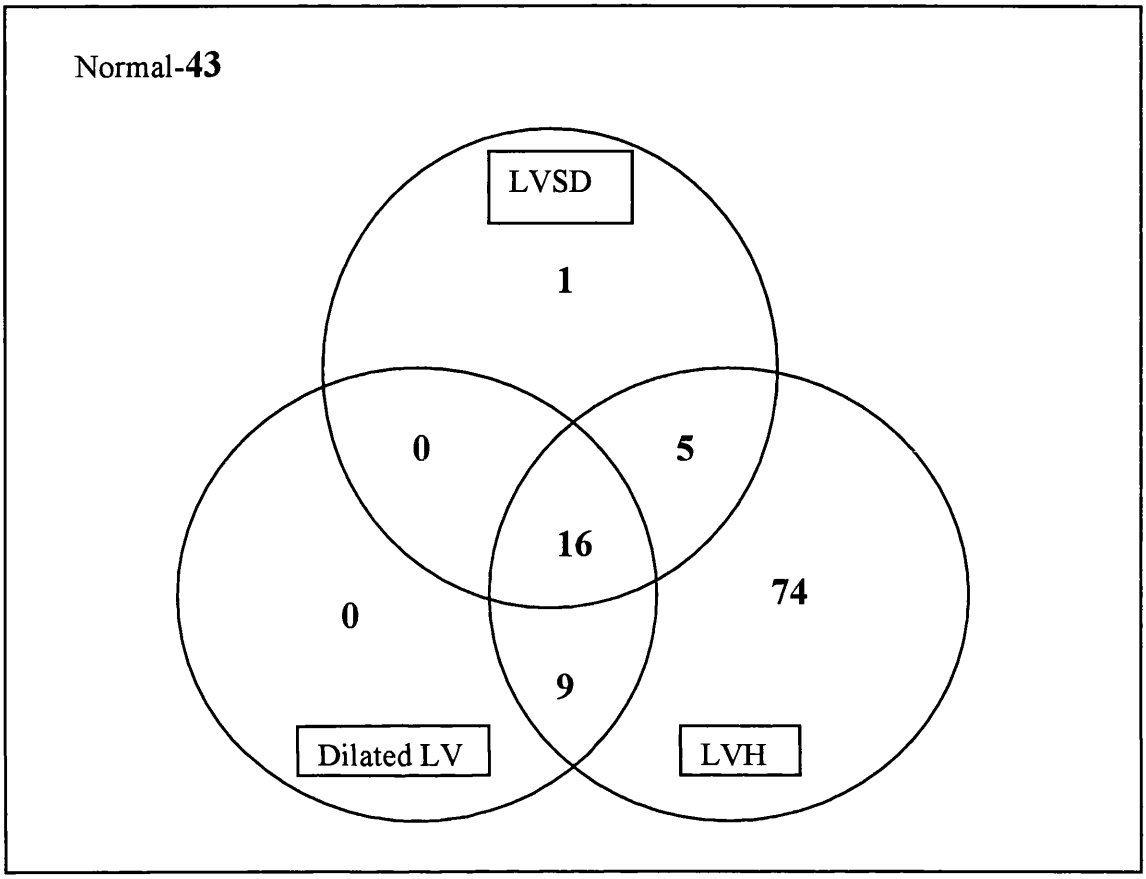
LVSV- left ventricular stroke volume

LVEF- left ventricular ejection fraction

LVM- left ventricular mass

Alfakih K, Plein S, Thiele H, Jones T, Ridgeway J, Sivananthan M. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient and steady state free precession imaging sequences. *Jnl Magn Res Imaging 17:323-329 (2003)*

Figure 4.1 Relationship of LV abnormalities in 148 patients with ESRF, felt suitable for renal transplantation, defined by CMR



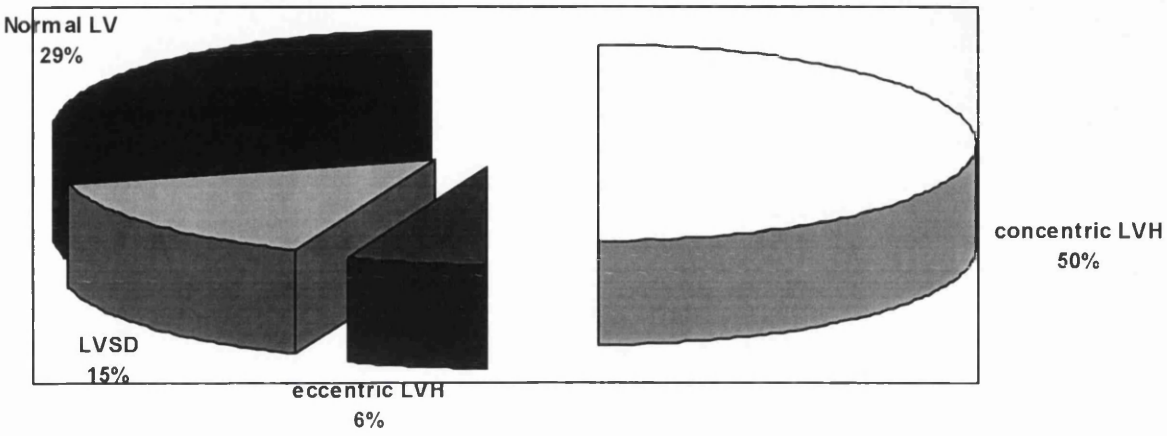
n=148

LVH- left ventricular hypertrophy

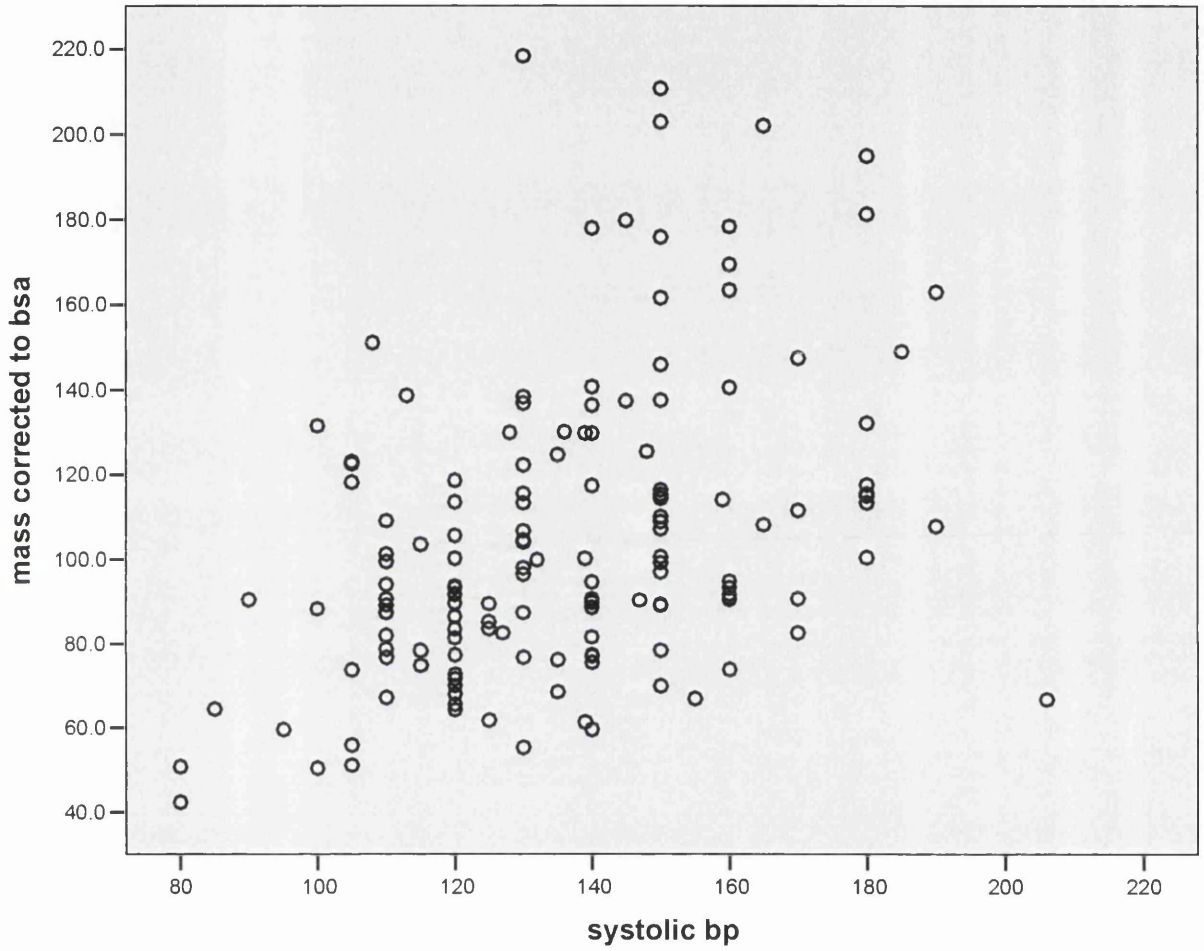
LVSD- left ventricular systolic dysfunction

Dilated LV- dilated left ventricle

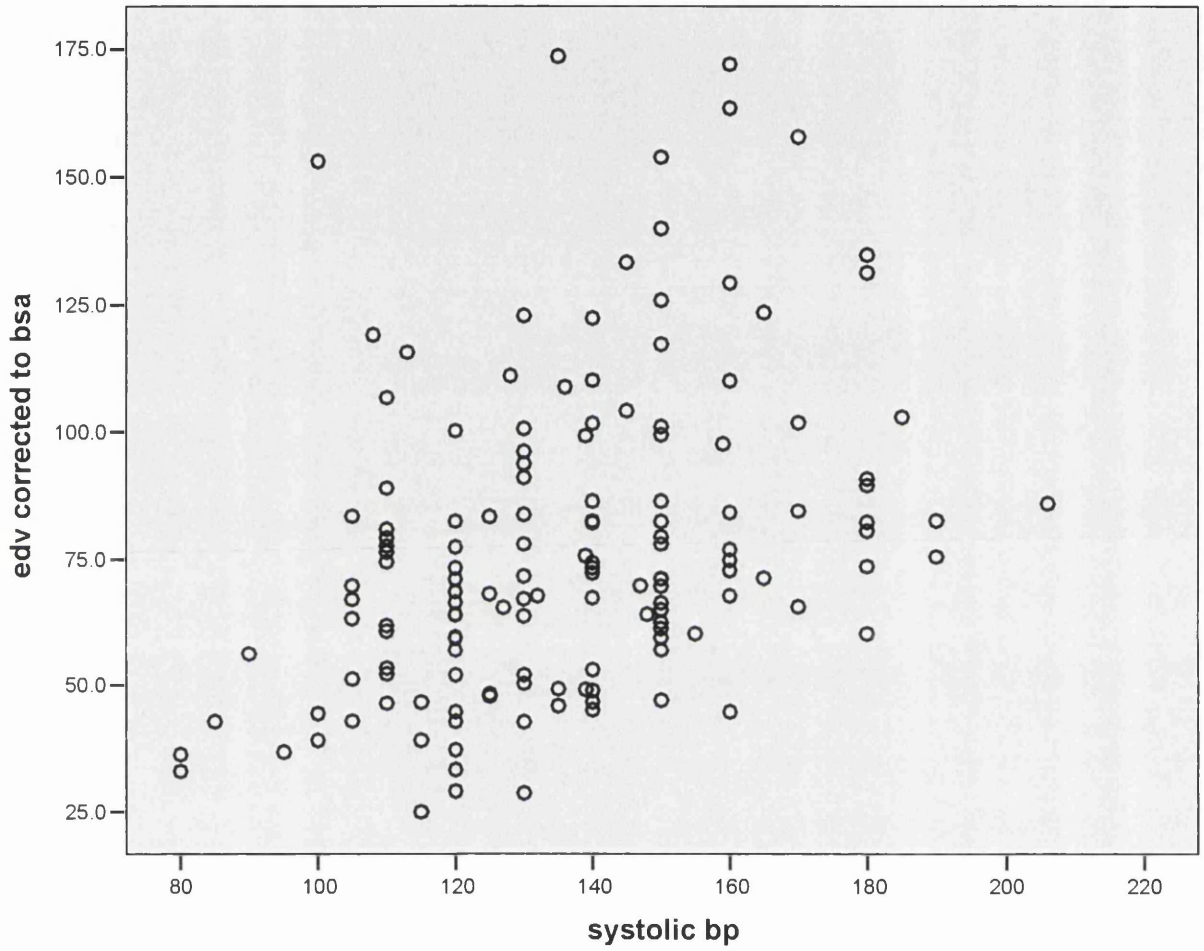
Figure 4.2 Piechart demonstrating prevalence of LV abnormalities in 148 patients with ESRF, felt suitable for renal transplantation, defined by CMR



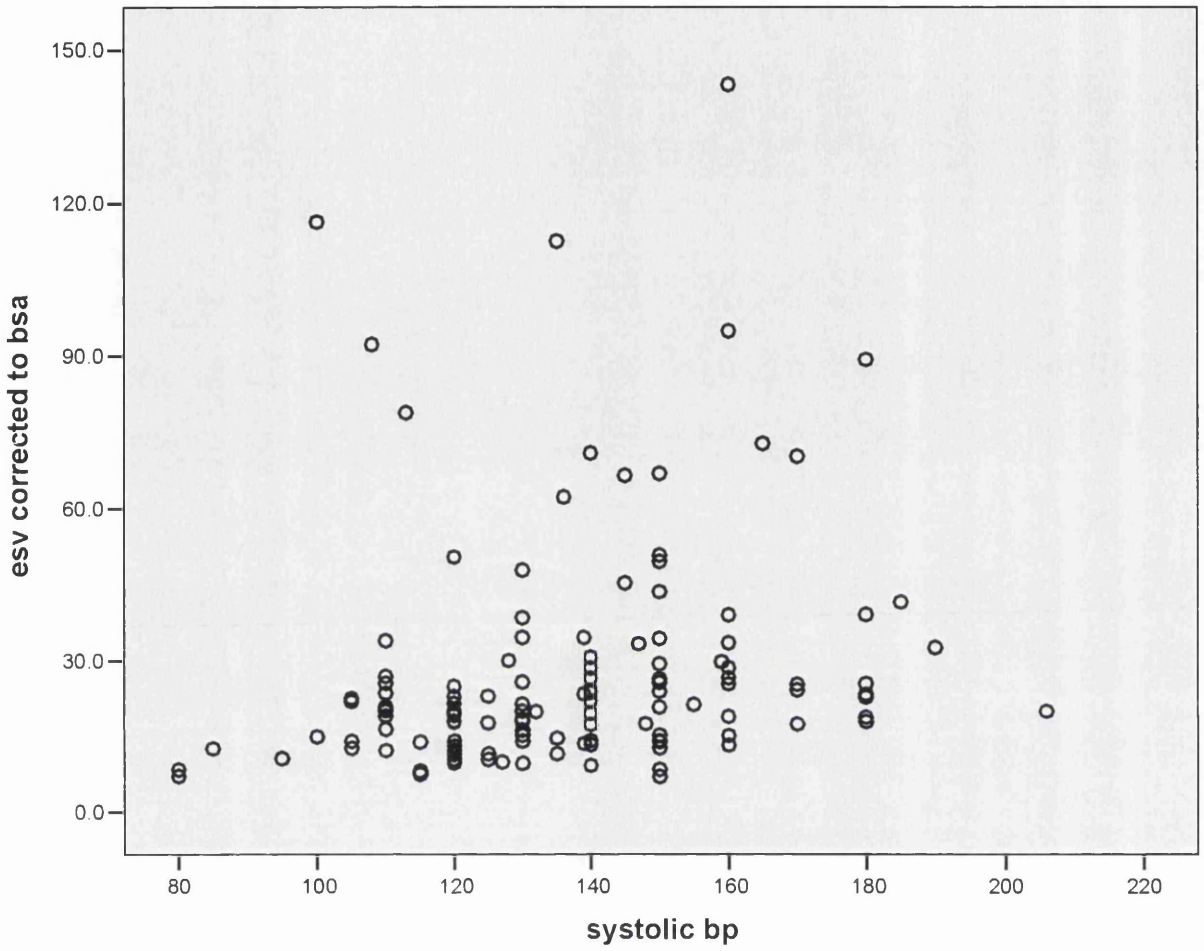
Graph 4.1 Scatterplot demonstrating correlation between systolic BP and LV mass corrected to BSA ($p<0.001$, $r=0.410$)



Graph 4.2 Scatterplot demonstrating correlation between systolic BP and EDV corrected to BSA ($p<0.001$, $r=0.374$)



Graph 4.3 Scatterplot demonstrating correlation between systolic BP and ESV corrected to BSA (p=0.023, r=0.201)



Graph 4.4 Scatterplot demonstrating correlation between systolic BP and Ejection Fraction (p=0.586, r=-0.046)

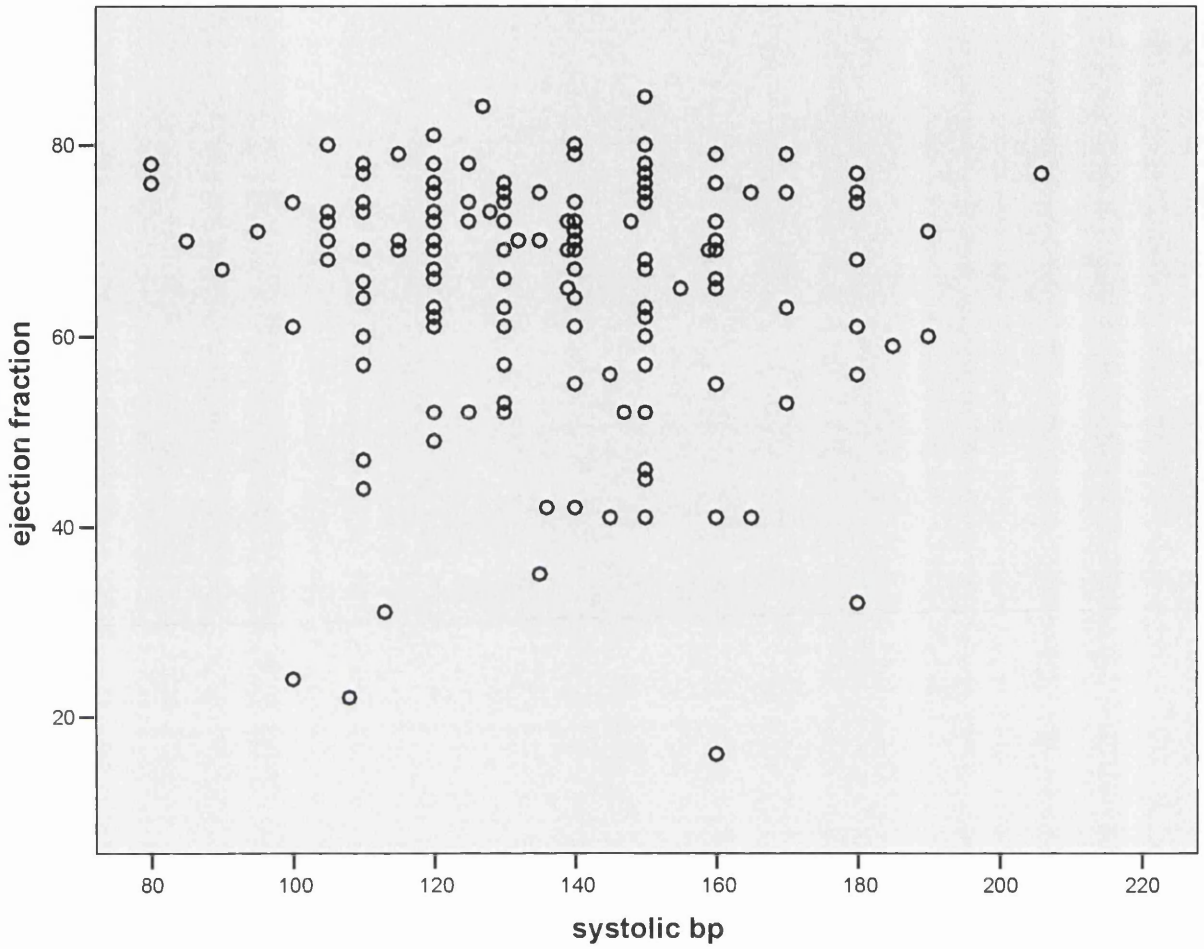


Table 4.2 Baseline characteristics of patients with different LV abnormalities

**p<0.05,abnormalLVvs.NormalLV;#p<0.05,LVHvs.NormalLV;*p<0.05,DilatedLVvs.NormalLV;##p<0.05,LVSDvs.NormalLV

Variable	*Normal LV n=43*	*Abnormal LV n=105*	*LVH n=74*	*LV dilated n=25*	*LVSD n=22*
Age(years)	50.7+/-10.1	50.2+/-11.1	50.0+/-11.1	45.2+/-9.5	53.8+/-10.3
Sex(% male)	57	72	67.6	81.8	87.0##
Length of RRT(months)	30.6+/-30	32.0+/-29	33.6+/-31	30.4+/-28	26.1+/-21.3
Hd vs. PD (% on PD)	45	61**	65.7#	60	60
Systolic BP (mmHg)	124.3+/-24.3	141.0+/-22.7**	140.7+/-23.6#	144.3+/-19.9*	136.9+/-22.2##
Diastolic BP(mmHg)	74.0+/-11.2	82.5+/-11.5**	82.8+/-11.9#	87.0+/-8.2*	78.7+/-10.6
PMH IHD (%)	12.2	26.8	11.3	27.3	45.5##
PMH CHF (%)	5.4	9.9	4.2	27.3*	22.7.0##
PMH DM (%)	11.0	26.8	15.3	9.1	50.0##
PMH HBP (%)	92	97	94.5	91	100
PMH other vascular (%)	0	10.0	5.6	12.0	18.2##
Smoker (%)	27	31	35.2	27	13.6##
High cholesterol (%)	36	35	33	36	42

Table 4.3 Mean LV parameters in patients with normal and abnormal left ventricles, defined by CMR

Variable	*Normal LV n=43*	*Abnormal LV n=105*	*p value*
Ejection Fraction (%)	69+/-6.8	63.8+/-14.3	p=0.003*
LVMI (g/m²)	71.9+/-12.7	118.1+/-32.1	p<0.001*
ESVcorrected to BSA (ml/m²)	16.7+/-5.8	32.6+/-25.8	p<0.001*
EDVcorrected to BSA (ml/m²)	56.8+/-17.8	85.4+/-30.3	p<0.001*
SVcorrected to BSA (ml/m²)	69.6+/-23.6	95.0+/-28.0	p<0.001*

*significant result with p<0.05

LVMI- left ventricular mass index

ESV- end-systolic volume

EDV- end-diastolic volume

SV- stroke volume

Table 4.4 Prescribed medication for patients with ESRF, felt suitable for renal transplantation, according to type of LV abnormality (* denotes significant p-value at $p<0.05$)

	Normal LV *n=43*	*Abnorm LV* *n=105*	*LVH* *n=74*	*DilLV* *n=25*	*LVSD* *n=23*
Aspirin (%)	24	35	27	18	71*
B Blocker (%)	26	40	39	45	43
ACEI (%)	17	25	15	45*	48*
Statin (%)	36	30	30	18	38
Mean no. of antihypertensives	1	1.4	1.3	1.5	1.6
Erythropoietin (%)	71	74	76	55	81

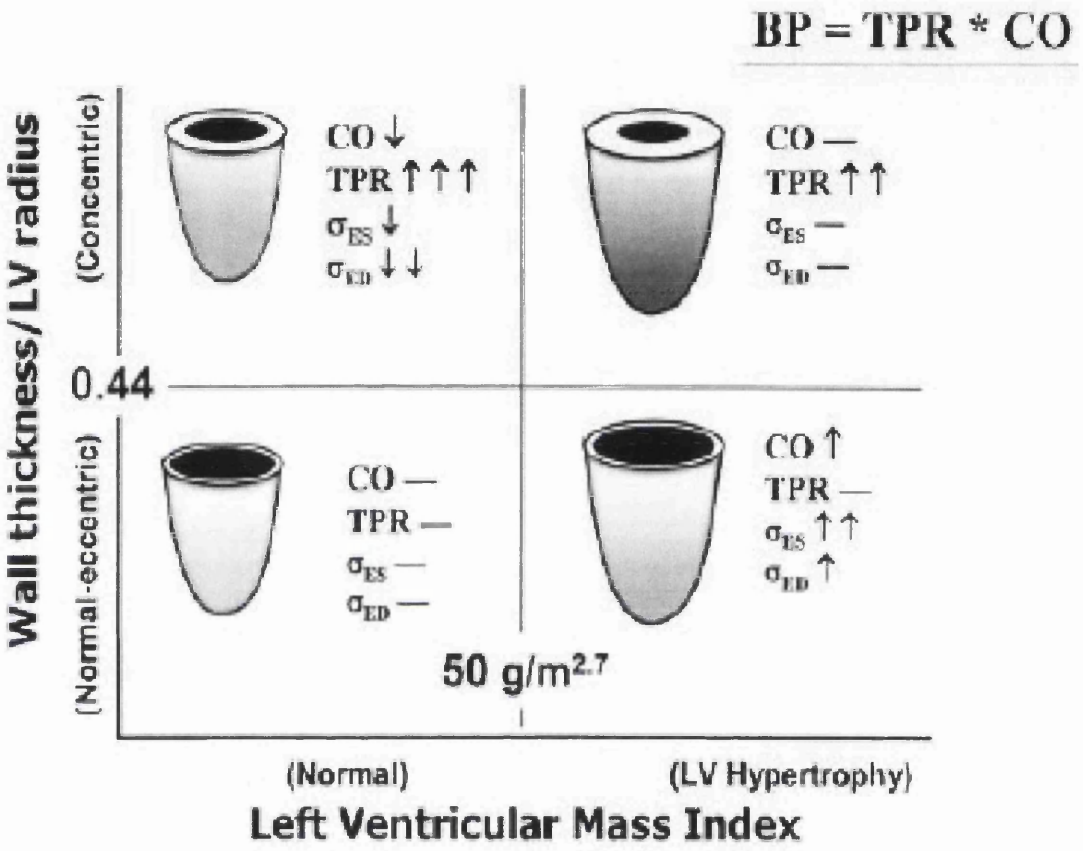
Table 4.5 ECG abnormalities in patients with LV abnormalities and ESRF (* denotes significant difference compared to those with a normal LV, $p<0.05$)

	Normal LV *n=43*	*Abnormal LV* *n=103*	*LVH* *n=74*	*LV dilated* *n=25*	*LVSD* *n=23*
ECGVariable					
Heart rate (bpm)	76+/-13	74+/-15	74+/-15	79+/-18	80+/-18
% with normal ECG	81	39*	44*	28*	100
LVH by voltage(%)	14.3	47*	46*	46*	50*
ST changes(%)	7.1	37*	26*	68*	69*
Q waves(%)	2.4	6.8*	2.8	23*	31*

Table 4.6. Independent determinants of LV abnormalities, defined by CMR, in patients with ESRF felt suitable for renal transplantation.

	LVMI	*EDV*	*ESV*	*EF*
Sex	p=0.002, β=0.220	NS	NS	NS
Systolic BP	NS	NS	NS	NS
Diastolic BP	p<0.001, β=0.293	p<0.001, β=0.301	NS	NS
HD as type of RRT	p=0.014, β=0.163	p=0.019, β=0.182	NS	NS
PMH of CHF	NS	p=0.003, β=0.236	p=0.037, β=0.175	p=0.006, β=-0.223
IHD	NS	NS	p=0.030, β=0.181	p=0.022, β=-0.186
Diabetes	p=0.004, β=0.202	NS	p=0.007, β=0.225	p=0.001, β=-0.266
lgBNP	p<0.001, β =0.373	p=0.002, β=0.250	p<0.001, β=0.367	p<0.001, β =-0.246

Figure 4.3 LV geometric patterns and proposed consequences of different combinations of pressure and/or volume overload (CO- cardiac output, TPR- total peripheral resistance, σ_{ES} – end systolic wall stress, σ_{ED} – end diastolic wall stress) (254-255)



Chapter 5

Natural history of Left Ventricular abnormalities in patients with ESRF awaiting Renal Transplant

5.1 Introduction

Several previous echocardiographic studies have suggested that LV abnormalities progress after instigation of dialysis (70,93,95). In the studies of Foley *et al.* (70), follow up of an initial cohort of 433 patients commencing RRT produced data on serial echocardiograms over 4 years for 29 patients. It was found that the natural history in this self-selected group was a continued increase in LVH and LVDil over time and that the mass:volume ratio remained constant suggesting the dominant evolutionary picture was one of progressive eccentric cardiomyopathy. It was also observed that most of the dilation took place in the first year of dialysis therapy and that haemodialysis as mode of RRT and anaemia were associated with ventricular enlargement. However, they did not find any significant deterioration of ventricular function, expressed as FS. In patients with predominant concentric LVH, progressive hypertrophy was the main finding and in those with eccentric LVH, continued LVDil occurred. These findings were in contrast to the study of Covic *et al.* (73) who found that concentric LVH rather than eccentric LVH was the main progressive pattern.

Subsequent to this Foley *et al.* have published further data on the serial changes of echocardiographic abnormalities in patients with ESRF (95). From the initial study, a cohort of 227 patients had baseline echocardiography at the instigation of dialysis and follow up echocardiography at a median interval of 13 months after the initial study and

were followed up for almost 4 years. Overall, a mean increase of LVMI mass was observed but patients were divided into groups depending on whether they showed individual increases or decreases in LVMI. Those that showed progression of LV mass had an increased incidence of new onset CHF compared to those whose LV parameters improved. Interestingly, no such differences were observed with LVDil and the authors concluded that serial echocardiograms added prognostic information over that of a single study and that a lag period of 2 years occurred before baseline LV abnormalities found at inception of dialysis therapy translated into the adverse outcome measure of CHF.

Subsequent work by Zoccalli *et al.* (93) has also shown that, in general, LV mass and LVDil progress in patients with ESRF on haemodialysis but that ventricular systolic function does not change significantly. Echocardiography was performed for 161 patients at baseline and after 18 months, with a further period of 29 months of follow up. Progression of LV mass was associated with an increased risk of death or incident CV event, independent of baseline LV mass and other risk factors.

Observational data therefore now suggests that, in general, LV mass progresses in patients on haemodialysis and that progression of LV mass implies a poorer outcome for that patient. However, why some patients on dialysis show progression of LV abnormalities and some show regression is unknown, although this is presumed to be due to an excess of risk factors associated with the initial development of LV abnormalities such as uncontrolled hypertension.

There are no studies detailing the natural history of LV abnormalities for the subgroup of patients on RRT awaiting renal transplant and whilst it is advised that patients undergoing

assessment for transplant should have yearly screening for IHD, no such guidelines exist for how often patients should have an assessment of LV structure and function.

Recently, the validity of longitudinal follow up studies using echocardiography has been brought into question with the establishment of CMR imaging (182-183,186,193,196-197). It has been suggested that studies requiring repeated measurements of LV mass or function in an individual should use CMR (203,259) as it has a superior inter and intra-observer variability and is more accurate than echocardiography. The use of CMR also means that either smaller sample sizes can be used to detect similar change or that changes can be detected over a shorter period of time in a similar sample size as that required for echocardiography. We therefore obtained 2 consecutive CMR scans, at least 6 months apart, with follow up data on LV mass, volumes and function in a cohort of 84 patients involved in our original study to investigate the natural history of LV abnormalities in patients awaiting renal transplant.

5.2 Methods

5.2.1 Subjects and Procedure

Patients were recruited from the West of Scotland renal transplant waiting list or directly from the renal transplant assessment clinic at the Western Infirmary, Glasgow. All patients gave informed consent and the study had approval from the local ethics committee. Screening procedure and methods are described in Chapter 2. Patients were contacted again 6 months after the date of initial screening and a further appointment was made for repeat scanning at the patient's convenience.

5.2.2 Statistics

Statistical analysis was performed using SPSS Version 11.5 software (SPSS inc. Chicago IL, USA). Baseline data are expressed as mean +/- SD or median, if not normally distributed. Differences between the groups were assessed using a two-sample t test (normally distributed data) or Mann Whitney U test (nonparametric data). A p-value of less than 0.05 was considered significant. 95% confidence intervals for differences between groups in mean percentage change from baseline are given. Correlations between continuous values were assessed using Pearson's correlation coefficient for parametric data.

5.3 Results

5.3.1 Baseline characteristics and prevalence of baseline left ventricular abnormalities

Data from two consecutive CMR scans at least six months apart were available for 84 patients and baseline characteristics are displayed in Table 5.1. Mean time of follow up scan was 8 months +/-1.2 months. Baseline characteristics were very similar to the initial cohort of 148 patients described in Chapter 3 and there were no significant differences in baseline data found between patients who attended for 2 scans and the initial cohort. Patients in the follow-up cohort were more likely to have undergone previous renal transplantation and had a slightly lower prevalence of heart failure than those in the initial cohort but these differences were not statistically significant.

Similarly, the prevalence and pattern of LV abnormalities at baseline was similar in the follow-up cohort as the initial group. LVH was the most frequently observed LV abnormality and was present in 66% of patients. LVSD was found in 15% of patients as was LVDil and 33% patients had a normal LV. Although the proportion of patients with normal ventricles was slightly higher in this smaller follow-up group compared to the baseline group, again this difference was not statistically significant and thus it was felt these 85 patients were representative of the initial cohort

5.3.2 Left ventricular abnormalities and follow up

The correlation between individual LV parameters at baseline and follow-up was good for all 4 parameters of Ejection Fraction (EF) ($p<0.001$, $r=0.769$), LV mass ($p<0.001$,

r=0.723), EDV (p<0.001, r=0.685) and ESV (p<0.001, r=0.842) and are shown in Graphs 5.1-5.3.

Initially LV abnormalities at baseline were compared with those on follow up for the entire cohort and are displayed in Table 5.2. Overall, there were no significant differences in any LV parameter at baseline and on follow up. The patients were then split into groups depending on whether a normal LV or an abnormal LV was found at baseline to ascertain whether there were any significant changes in LV parameters within these groups over time.

5.3.3 Follow-up changes in patients with normal left ventricles at baseline

Just over one third of patients (29 patients) in the cohort had a normal LV on baseline scan and data on LV parameters at baseline and follow-up are displayed in Table 5.3. Interestingly, although EF (p=0.322), ESV (p=0.618) and EDV (p=0.979) did not change significantly on follow up, LV mass did increase significantly from 76.8+/-14.9g/m^2 to 84.0+/-18.6g/m^2 (p=0.009) in those with an initially normal LV (Graph 5.8).

5.3.4 Follow-up changes in patients with an abnormal LV at baseline

Again, LVH was the most frequent LV abnormality observed and a total of 66% of patients had LVH on baseline CMR scan. Almost all patients with an abnormal LV in the cohort had LVH and therefore this includes those patients with associated LVSD and LVDil. Results of LV parameters at baseline and follow up are displayed in Table 5.4. In contrast to those with normal ventricles at baseline, no significant differences were seen

on follow-up in those patients who already had an abnormal LV with regard to any of the LV parameters measured.

5.3.4 Follow-up changes in patients with isolated LVH at baseline

Concentric LVH was the most common LV abnormality observed in the cohort. Forty patients in the cohort had concentric LVH on the baseline scan and made up 46.4% of the total cohort. Differences on baseline scan and follow up as shown in Table 5.5. Again, no significant differences were observed in LV parameters at baseline and follow up and total LV mass actually decreased slightly with follow-up but this difference did not reach statistical significance.

5.3.5 Follow-up changes in patients with LVSD

Ten patients were found to have LVSD at baseline scan (12% of cohort) and all of these also had a dilated ventricle and associated LVH. With follow-up after at least 6 months, no differences were found in LV function, volumes or mass in this group. Results of the analysis between baseline and follow-up scan are shown in Table 5.6.

5.3.6 Follow-up changes in LV parameters in individuals

Within the cohort as a whole there were no significant differences observed with any LV parameter measured. However, more interesting individual differences in patients at baseline and follow up are described in Table 5.7 and displayed in Graphs 5.4-5.6 for EF, LV mass corrected to BSA and EDV corrected to BSA respectively.

The only significant difference observed with follow up was an increase in LV mass in those who had a normal LV at baseline. There were 29 patients (34.5%) in the cohort with a normal LV at baseline and with follow up 13 of these patients (45% of those with an initial normal LV) developed LVH whilst 1 patient with an initially normal ventricle developed LVSD after an anterior AMI.

Conversely, 9 patients in the group with initial concentric LVH showed apparent regression to normal mass and volumes, although 5 of these patients may actually be better categorized into the group of concentric remodelling described by Ganau *et al.* (Figure 4.2) (253). Four patients with initial concentric LVH progressed to eccentric LVH and no changes were observed with regard to patients in the group with LVSD. The group with eccentric LVH was small (6 patients), the majority of which showed no change.

Individual changes in LV mass in patients with an initial normal LV are displayed in Graphs 5.7-8. Baseline characteristics including baseline LV mass, EDV, ESV and EF were compared between those who developed LVH on follow up and those whose ventricles remained normal. The only significant difference between the 2 groups was the prevalence of diabetes ($p=0.040$). (Table 5.8).

As noted above, 13 patients were observed to undergo progression of LVH to develop abnormal ventricles and 10 patients with abnormal ventricles, all of which had initial concentric LVH underwent progression of LVH by >/= $10g/m^2$. In contrast 9 patients with abnormal ventricles at baseline underwent regression of LVH by >/=$10g/m^2$. Baseline variables of these two groups were also compared and the only significant difference between those with progression of LVH and those with regression of LVH was

baseline LV mass (p=0.017). Those demonstrating regression had a higher LVMI compared to those demonstrating progression (117.7+/-28.0g/m^2 vs. 90.4+/-24.9g/m^2) Interestingly, there were no significant differences with regard to baseline BP in either patients who developed an abnormal LV or those with initially abnormal ventricles that showed progression or regression of LVH.

5.4 Discussion

The number of patients selected for renal transplant continues to rise and includes an increasing proportion of older patients and those with additional co-morbidity. As a consequence, waiting times for a cadaver donor kidney have become longer and in the future a significant proportion of patients will wait 3-5 years for transplant (260). Indeed, on average, patients in this cohort had been on dialysis for almost 3 years.

The American Society of Transplantation published guidelines in 2002 (261) suggesting those at high risk of CV disease should undergo repeated 'imaging' studies to rule out progression of overt IHD during the waiting period. This guideline was not more specific as it was acknowledged there was a lack of studies addressing patients on the waiting list. The presence of LVH was defined in these guidelines as a 'high risk' marker and if LVH was found in the presence of another risk factor, such as age >45 or male sex, patients should undergo annual screening and these guidelines are very similar to those of the UK based Renal Association (244-245). However, while progression of LV abnormalities in patients on RRT is well described, there is much less data detailing the natural history of LV abnormalities in the sub-group waiting for renal transplant and if patients were to develop LVH whilst on the waiting list that could convert status from 'normal' risk to 'high' risk.

In this study, we acquired data on 84 patients felt suitable for renal transplant and followed up a baseline CMR study with another study after a mean period of 8 months. Overall, there were no significant changes in LV parameters between baseline and follow-up study which is not entirely surprising given the relatively short follow-up time. However, when the groups were split into those who had a normal LV at baseline and

those who had an abnormal LV, an interesting difference did occur. Although LV parameters in the group with an abnormal baseline LV did not change significantly with follow up, those with an initially normal ventricle showed a significant progression of LV mass and 45% patients with an initially normal ventricle developed an abnormal LV through development of concentric LVH. Thus, with follow up, degree of CV risk in this group increases.

When this group of patients exhibiting progression of LVH was compared to those whose ventricles remained normal, the only significant difference between groups was prevalence of diabetes. No diabetic patients were found in the group whose ventricle remained normal, whereas 25% of patients who showed progression of LVH were diabetic. However, the numbers in the groups were small (11 vs. 15) and this result should be interpreted with caution as should the lack of difference found in other variables such as BP, which although was higher in the group who developed LVH, was not statistically significant..

Individual differences with regard to EF and volumes were generally small and as mentioned previously, only one patient had a significant drop in EF and increase in volumes after a large AMI. This finding is in keeping with the findings of Foley *et al.* (95) and Zocalli *et al.* (93). However, previous echocardiographic studies have found significant individual changes with regard to LV volumes and dilation. In this study we found no such differences but the number of patients categorized with eccentric LVH was small which may have affected analysis. Our findings suggest that any changes over time observed with EF and LVDil occur more slowly than the rate change of LV mass or, in the case of EF, produced by events such as AMI. However, with follow-up the

proportion of patients with normal ventricles fell from 34.5% to 28.5%, although this difference was not found to be statistically significant.

Only significant progression or regression of LVMI was observed over a period of 8 months in this cohort. In the group of patients with concentric LVH, 10 showed progression of LVH and 9 showed regression of LVH by >/=10g/m^2. When patients who showed progression during the study were compared with those showing regression, the only significant difference was baseline LV mass. Patients showing progression of LVH were more likely to have a lower LV mass at baseline scan than those showing regression. It is unclear why this should be the case but again, small groups and the relatively larger variability of those with elevated LV mass may affect these results and have led to the phenomenon of regression to the mean.

In the early studies of Foley *et al.* ventricular enlargement was mainly observed in the first 12 months of RRT, with relatively little further change thereafter. This was not the case in this cohort. Average time on RRT was almost 3 years and there were no significant differences observed with regard to time on RRT between those who displayed progression or regression of LV parameters and those who showed no change. This suggests that intervention in patients awaiting renal transplantation to reduce LV mass is feasible.

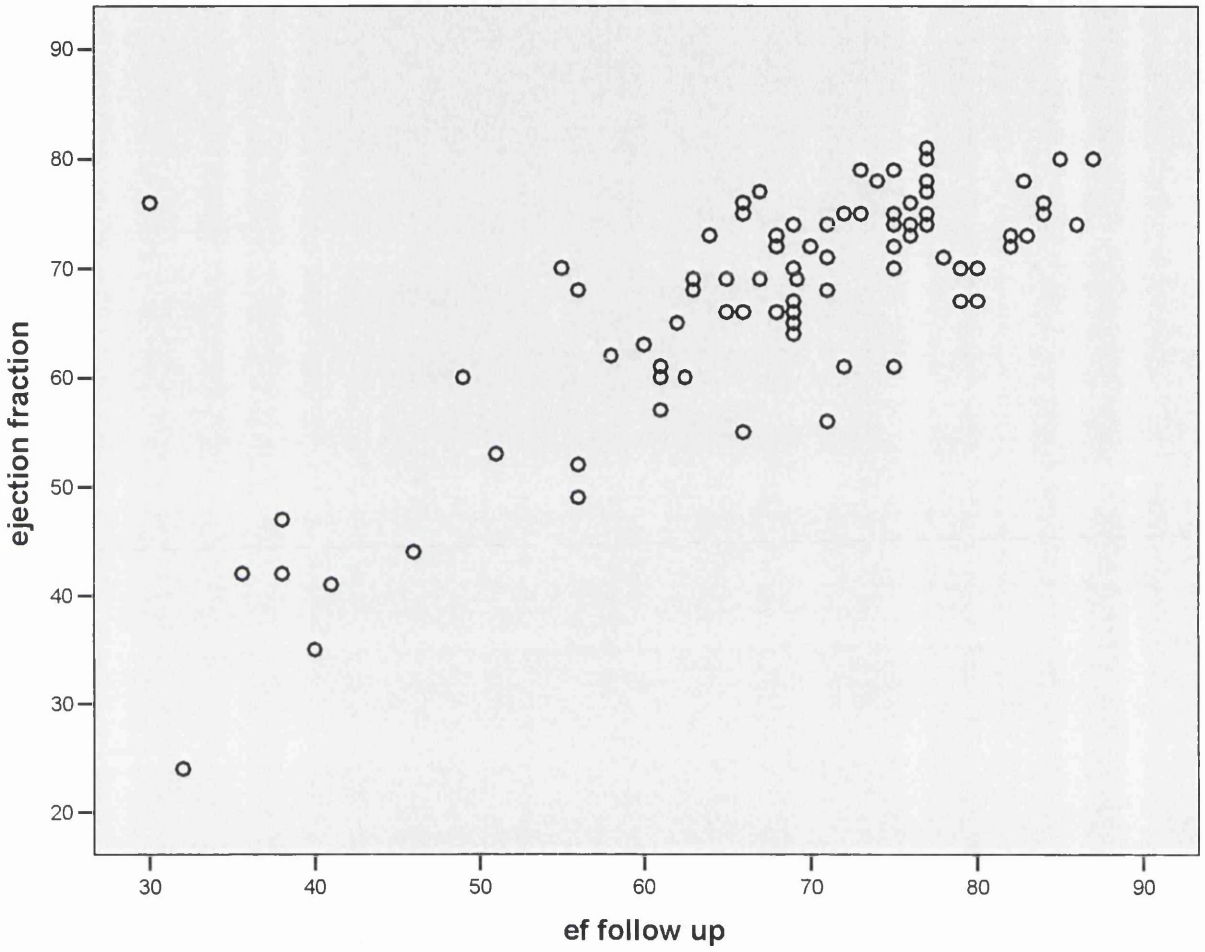
Within a relatively short period of follow up, a significant proportion of patients developed concentric LVH after an initial low risk screening scan. Apart from a history of diabetes, no clear differences existed to identify those who progressed from a normal LV to an abnormal LV. Although the numbers in this study are relatively small, the patients were representative of the initial larger cohort and suggest that lower risk patients

can progress to higher risk in under a year. Zoccalli *et al.* observed that progression of LVH in patients on RRT was associated with a higher incidence of CV events and a higher mortality after 2 years of follow-up. The findings of this study may have implications for management of renal transplant waiting lists, especially as average waiting time increases and warrants further study, both to replicate initial findings in a larger patient group over a longer time period and to examine whether progression of LV mass whilst on the transplant waiting list translates into a poorer long term outcome.

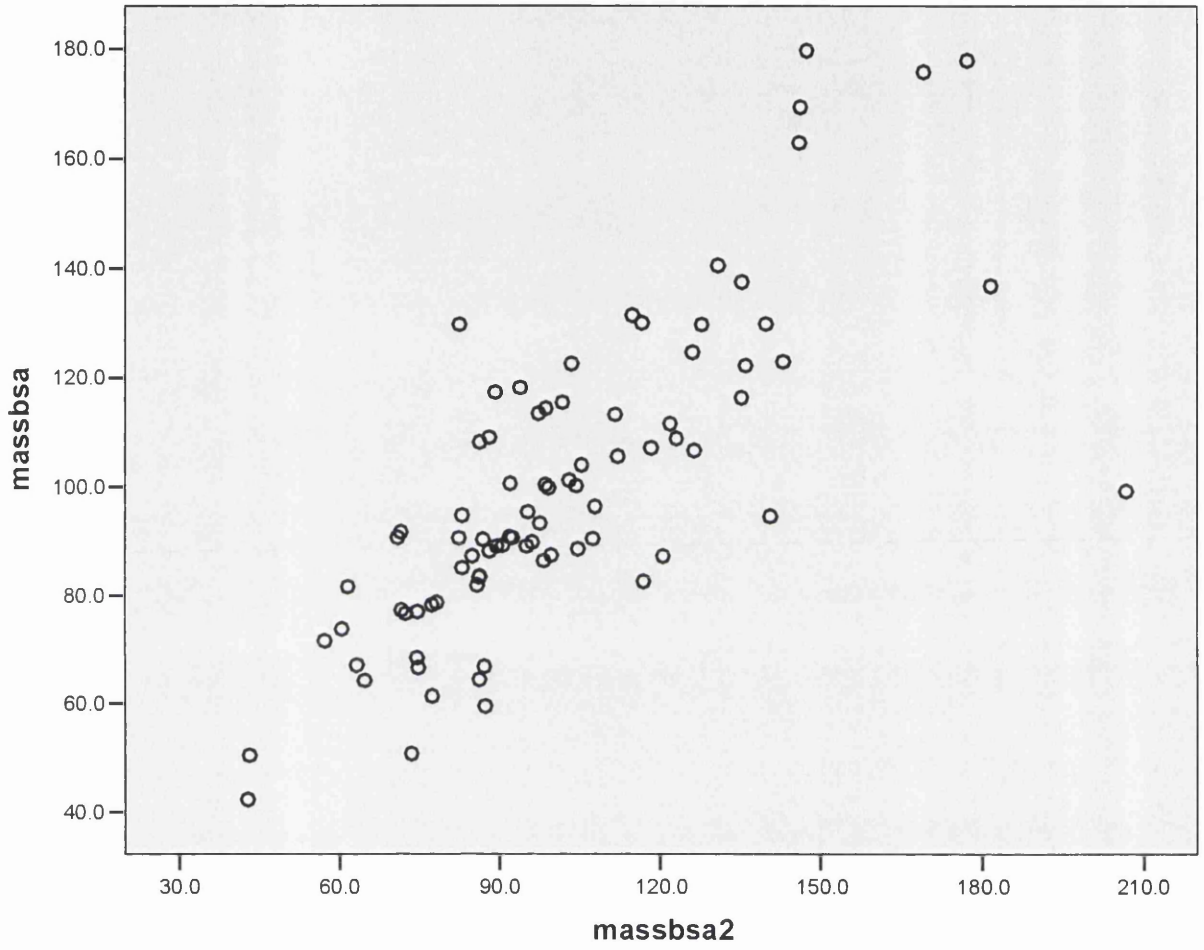
Table 5.1 Baseline demographics of 84 patients undergoing CMR follow-up

BASELINE VARIABLE	**Follow-up cohort n=84**	**Initial cohort n=148**	**p value**
Age (years)	51 +/-10	50+/-10	0.89
Sex (%male)	62.4	68.2	0.64
Patients on haemodialysis (%)	62	60	0.92
Length of time on RRT (months+range)	34.6 (0-144)	31.6 (0-144)	0.66
Length of renal failure (yrs+range)	12.6 (2-45)	8.2 (0.2-39)	0.63
Previous renal transplant (%)	22.8	18.2	0.12
History of Ischaemic Heart Disease (%)	21.4	19.3	0.43
Previous myocardial infarction (%)	8.6	9.7	0.87
History of chronic heart failure (%)	4.8	7.6	0.69
Diabetic (%)	16.7	18.6	0.48
History of hypertension (%)	91.7	94.5	0.88
History of hyperlipidaemia (%)	36	36	0.98
Current smoker (%)	27.7	29.2	0.58
Systolic blood pressure (mmHg+/-95%CI)	134+/-24	136+/-24	0.64
Diastolic blood pressure (mmHg+/-95%CI)	78+/-12	80+/-12	0.67
Cholesterol level (mmol/L+/-95%CI)	5.6+/-1.5	5.6+/-1.7	0.89
Haemoglobin (g/dL+/-95%CI)	11.6+/-1.4	11.5+/-1.6	0.92

Graph 5.1 Scatterplot demonstrating correlation between Ejection Fraction at baseline and follow-up ($p<0.001$, $r=0.769$)



Graph 5.2 Scatterplot demonstrating correlation between LV mass at baseline and follow-up ($p<0.001$, $r=0.723$)



Graph 5.3 Scatterplot demonstrating correlation between ESV at baseline and follow-up ($p<0.001$, $r=0.842$)

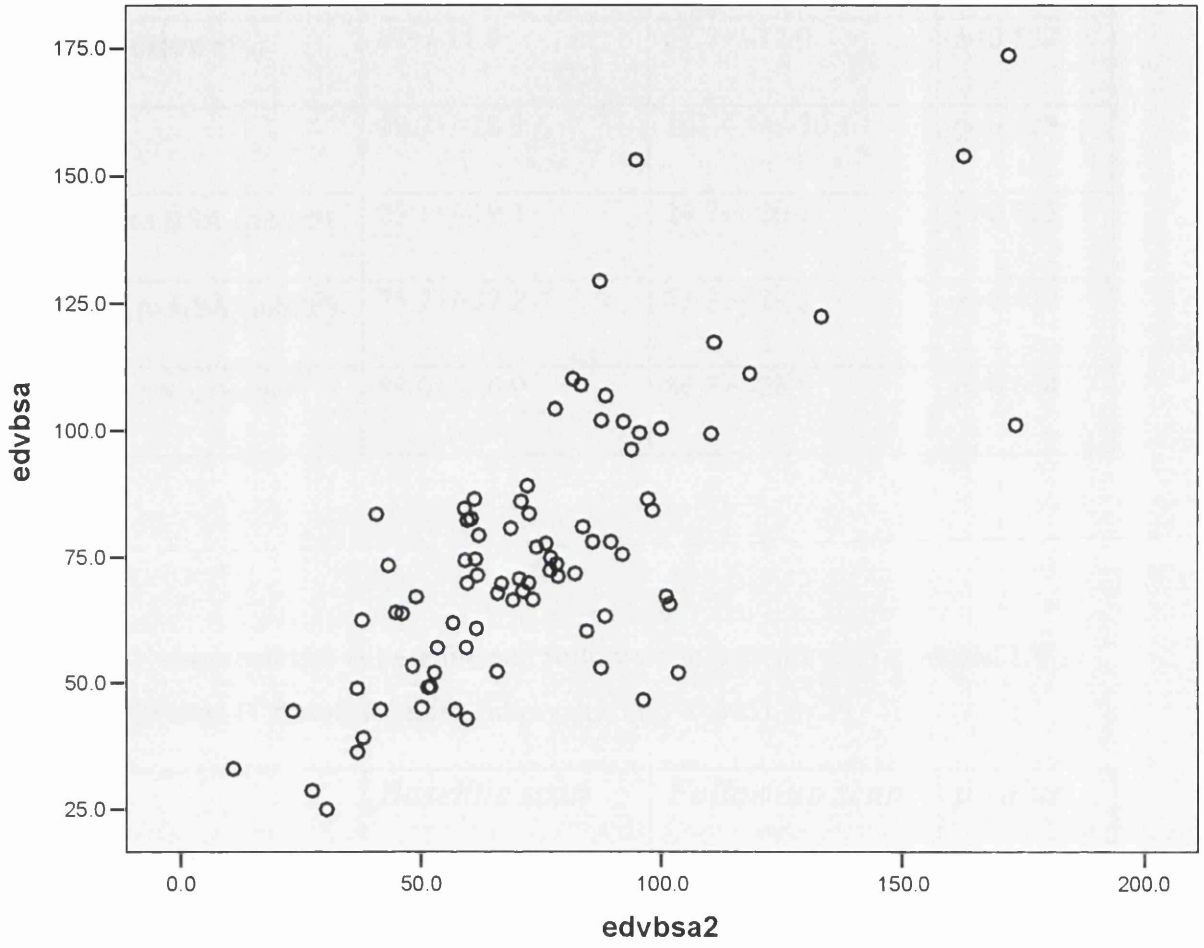


Table 5.2 LV abnormalities at baseline and follow-up in 84 patients with ESRF, felt suitable candidates for renal transplantation

Variable	*Baseline scan*	*Follow-up scan*	*p value*
Ejection Fraction (%)	67+/-11.0	67.7+/-12.0	p=0.527
LVMI (g/m^2)	99.7+/-28.3	101.4.1+/-30.1	p=0.428
ESVcorrected to BSA (ml/m^2)	25.1+/-19.1	24.7+/-20.1	p=0.825
EDVcorrected to BSA (ml/m^2)	75.7+/-27.2	73.9+/-29.3	p=0.419
SVcorrected to BSA (ml/m^2)	88.0+/-26.9	86.7+/-26.9	p=0.604

Table 5.3 LV abnormalities at baseline and follow-up in patients with a normal LV at baseline CMR scan (* denotes significant p-value at $p<0.005$). n=29

Variable	*Baseline scan*	*Follow-up scan*	*p value*
Ejection Fraction (%)	69+/-6.2	71+/-9.3	p=0.322
LVMI (g/m^2)	76.8+/-14.9	84.0+/-18.6	p=0.009*
ESVcorrected to BSA (ml/m^2)	17.8+/-6.5	18.6+/-9.5	p=0.618
EDVcorrected to BSA (ml/m^2)	60.4+/-18.6	60.3+/-22.7	p=0.979
SVcorrected to BSA (ml/m^2)	95.8+/-24.8	91.8+/-25.9	p=0.172

Table 5.4 LV abnormalities at baseline and follow-up in patients with an abnormal LV at baseline CMR scan. n=55

Variable	*Baseline scan*	*Follow-up scan*	*p value*
Ejection Fraction (%)	66+/-12.8	66+/-13.5	p=0.910
LVMI (g/m²)	111.7+/-26.1	110.9+/-30.7	p=0.777
ESVcorrected to BSA (ml/m²)	28.9+/-22.2	27.9+/-23.3	p=0.713
EDVcorrected to BSA (ml/m²)	83.8+/-27.7	81.1+/-30.0	p=0.345
SVcorrected to BSA (ml/m²)	95.7+/-24.8	91.8+/-25.9	p=0.172

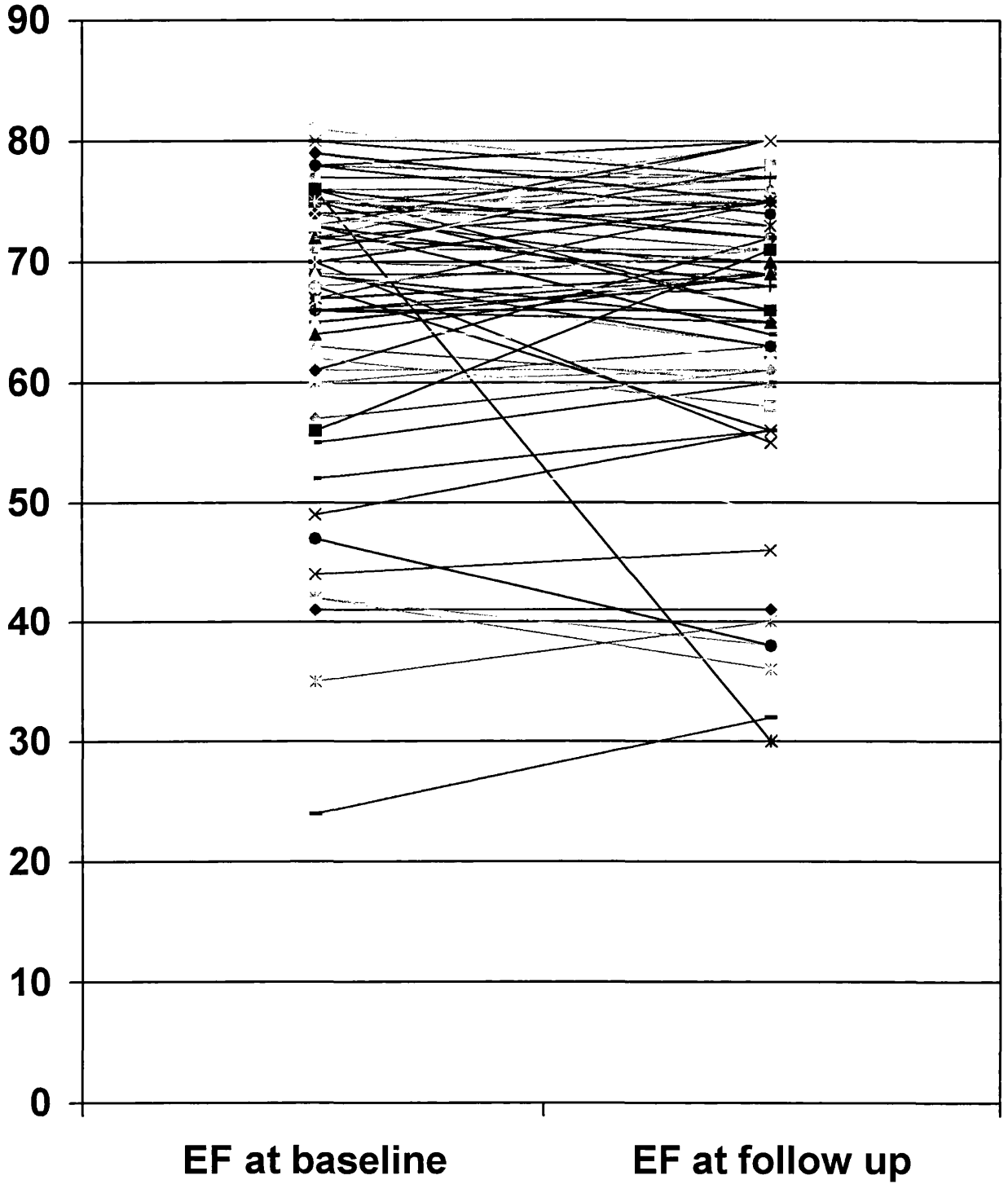
Table 5.5 LV abnormalities at baseline and follow-up in patients with isolated LVH at baseline CMR scan. n=40

Variable	*Baseline scan*	*Follow-up scan*	*p value*
Ejection Fraction (%)	71.9+/-5.2	71.9+/-7.1	p=0.981
LVMI (g/m²)	104.4+/-18.9	101.5+/-25.3	p=0.243
ESVcorrected to BSA (ml/m²)	19.1+/-6.0	18.2+/-8.0	p=0.441
EDVcorrected to BSA (ml/m²)	70.3+/-15.1	67.7+/-18.4	p=0.340
SVcorrected to BSA (ml/m²)	90.1+/-19.8	87.9+/-26.4	p=0.432

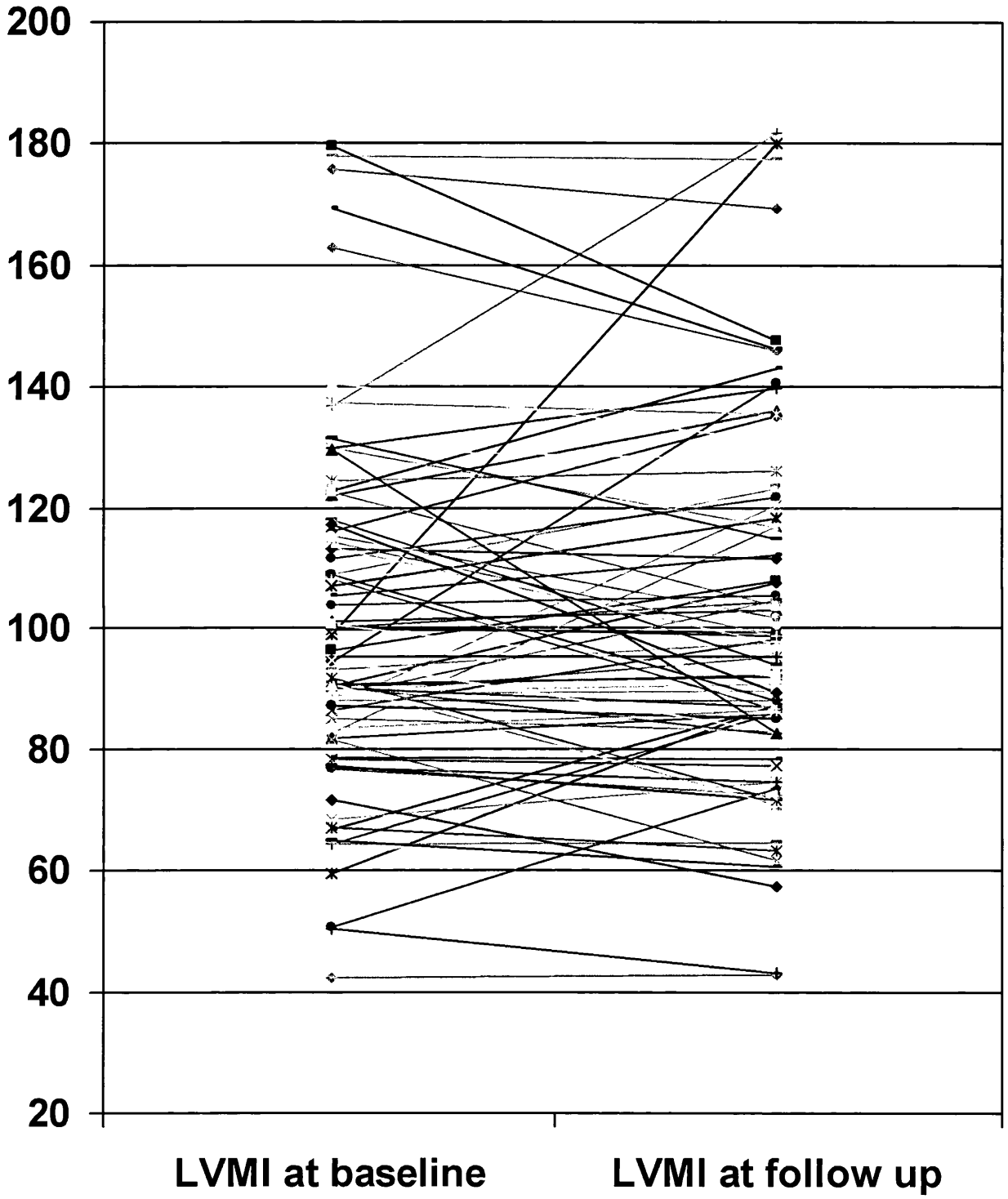
Table 5.6 LV abnormalities at baseline and follow-up in patients with LVSD at baseline CMR scan. n=10

Variable	*Baseline scan*	*Follow-up scan*	*p value*
Ejection Fraction (%)	47.5+/-12.4	45.9+/-9.1	p=0.245
LVMI (g/m^2)	116.6+/-27.9	117.6+/-33.2	p=0.810
ESVcorrected to BSA (ml/m^2)	58.3+/-28.9	62.0+/-32.4	p=0.122
EDVcorrected to BSA (ml/m^2)	102.2+/-35.7	108.2+/-36.1	p=0.246
SVcorrected to BSA (ml/m^2)	85.1+/-21.6	87.1+/-20.7	p=0.620

Graph 5.4 Changes in Ejection Fraction in individual patients at baseline and follow-up



Graph 5.5 Changes in LVMI in individual patients at baseline and follow up



Graph 5.6 Changes in EDV in individual patients at baseline and follow-up

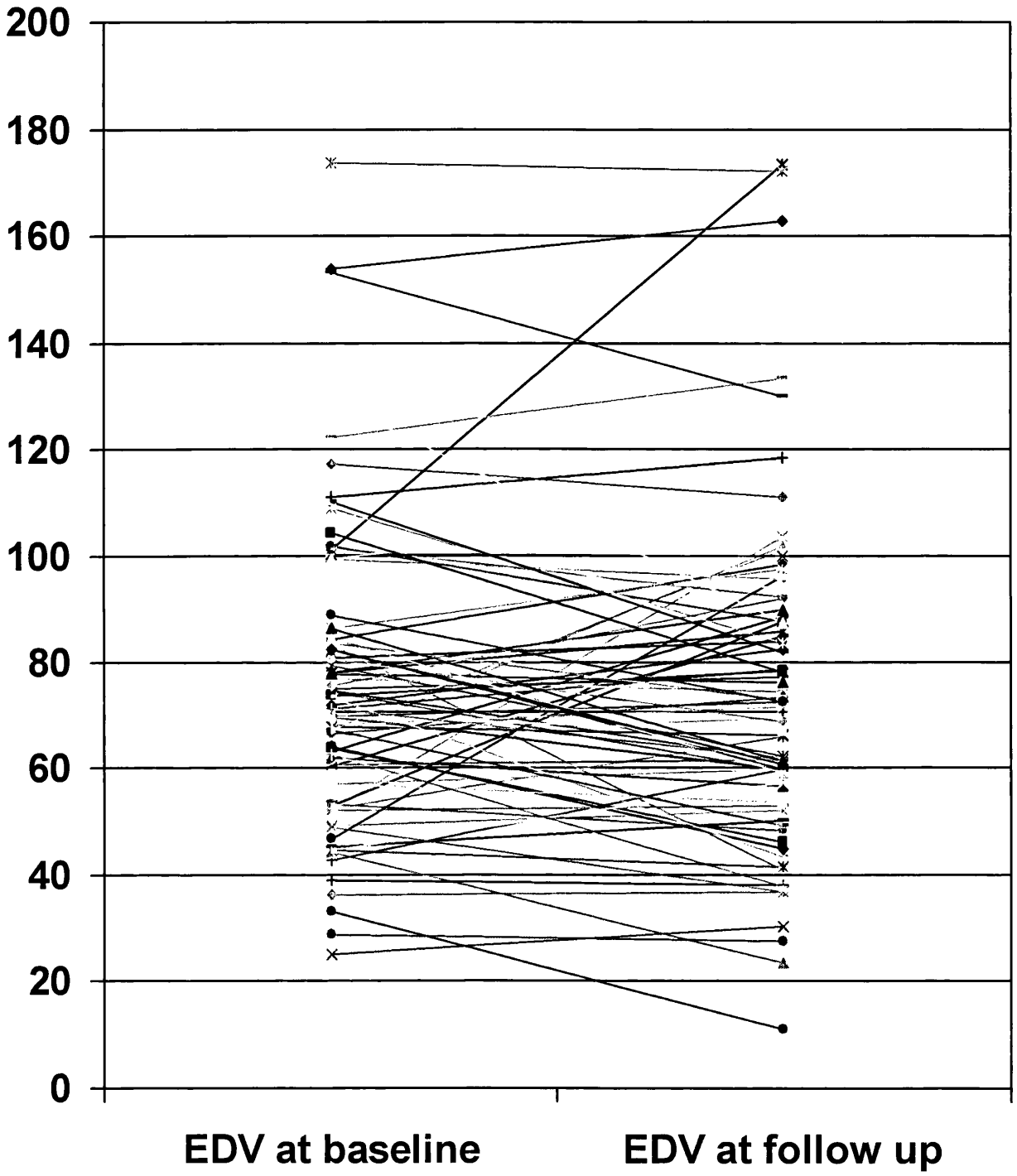
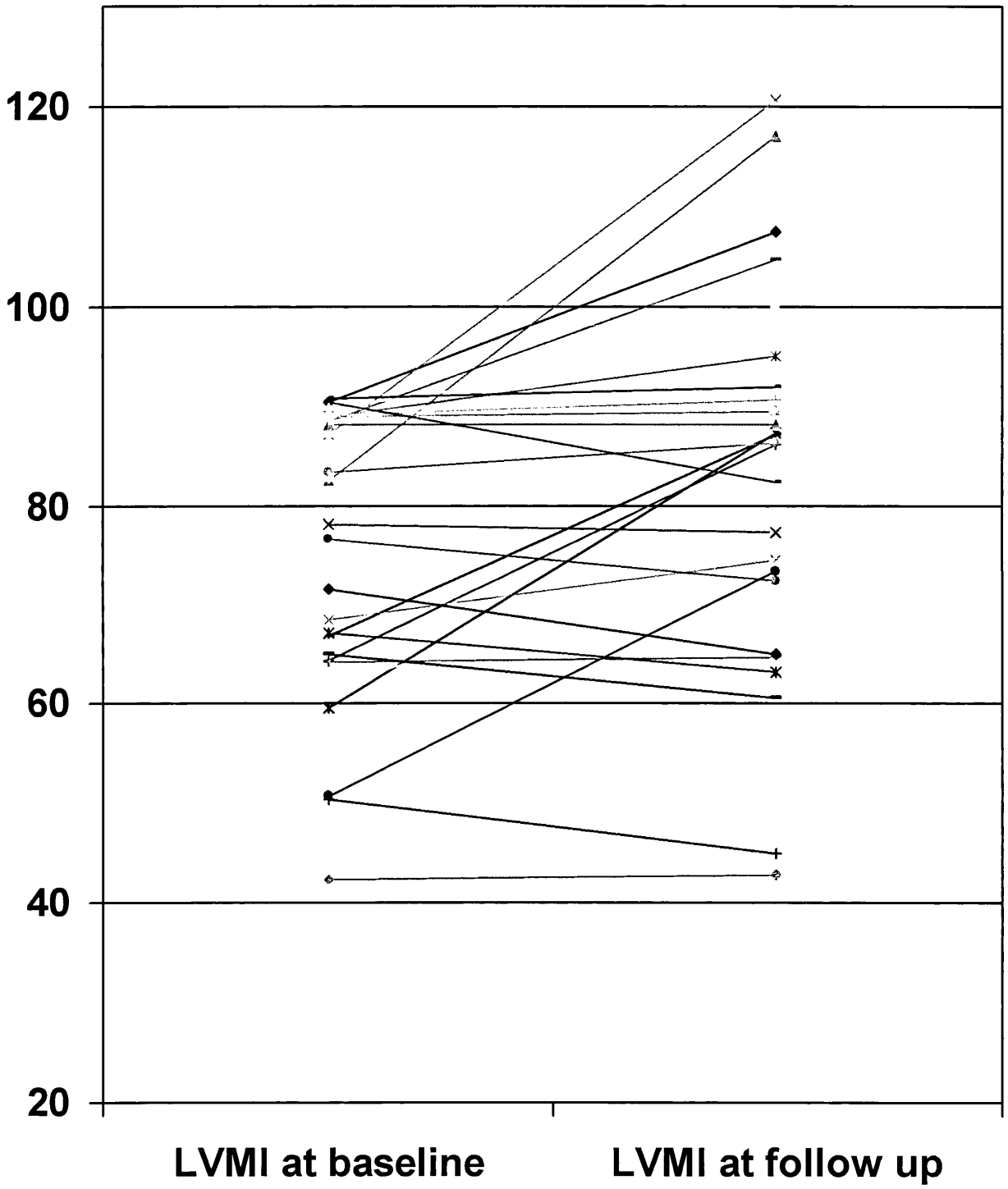


Table 5.7 Individual changes in LV parameters after 8+/-1.2 months (percentage difference from baseline findings)

First Scan	Second Scan				First Scan % of total cohort
	Normal	***Concentric LVH***	***Eccentric LVH***	***LVSD***	
Normal	**15 (52%)**	**13 (45%)**	**0**	**1 (3%)**	34.5%
Concentric LVH	**9 (23%)**	**26 (67%)**	**4 (10%)**	**0**	46.4%
Eccentric LVH	**0**	**1 (17%)**	**4 (66%)**	**1 (17%)**	7.1%
LVSD	**0**	**0**	**0**	**10 (100%)**	12%
Second scan % of total cohort	28.5%	47.6%	9.5%	14.4%	

Graph 5.7 Change in LVMI in individual patients with a normal LV at baseline (p=0.009)



Graph 5.8 Error plot showing difference in baseline LV mass and follow-up LV mass in those with a normal LV at baseline (p=0.0009)

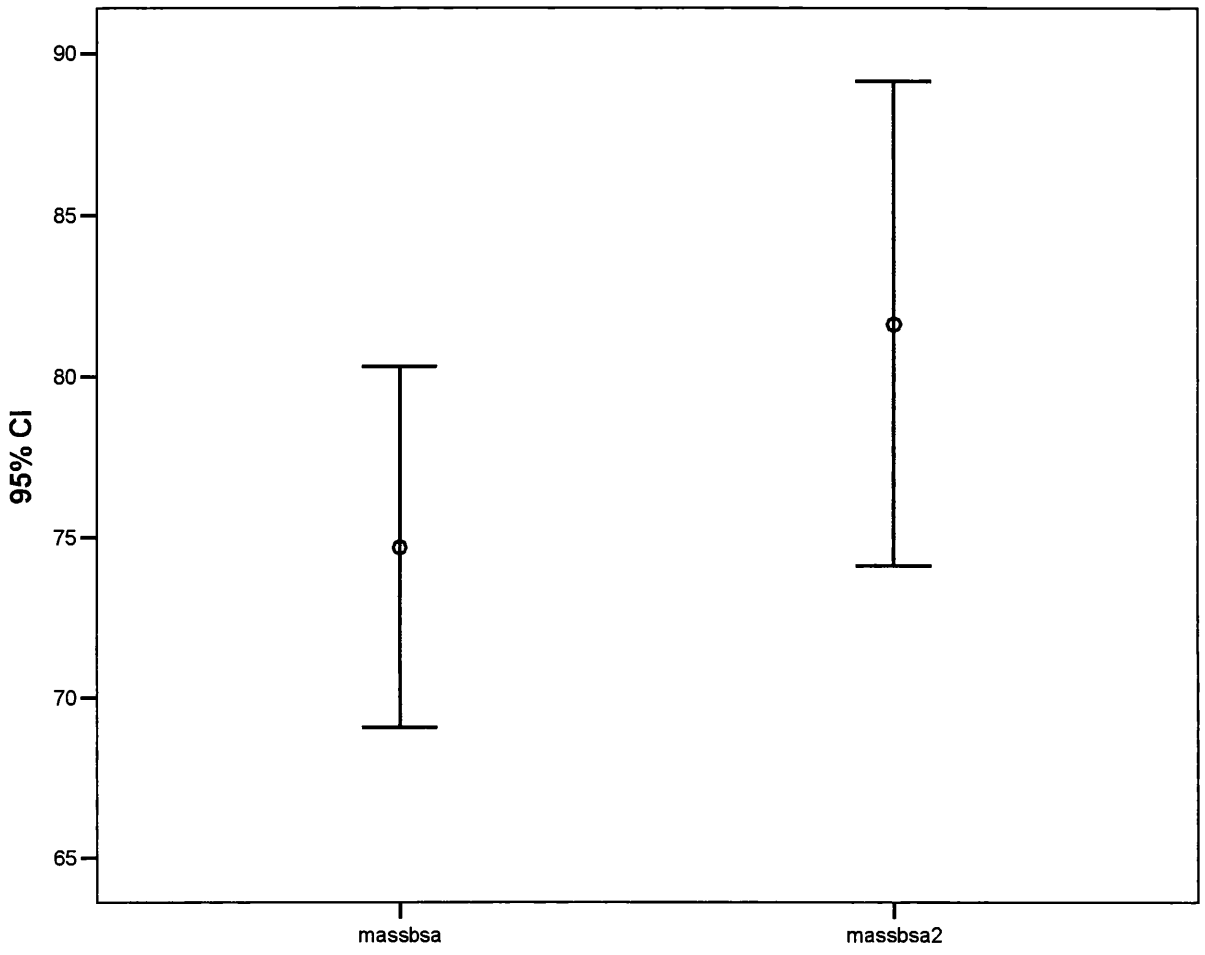


Table 5.8 Differences in baseline characteristics between patients who developed LVH on follow-up and those whose ventricles remained normal. * denotes $p<0.05$

Variable	*Normal LV on follow up (n=15)*	*LVH on follow up (n=13)*	*p value*
Age (years)	49.7+/-12.0	52.6+/-8.1	p=0.473
Sex (%male)	60	58	p=0.943
Patients on haemodialysis (%)	53	58	p=0.683
Time on dialysis (months)	41.5+/-32.3	31.9+/-33.0	p=0.454
Length of renal failure (yrs)	13.5+/-5.6	11.0+/-13.6	p=0.518
History of IHD (%)	20	15	p=0.687
Diabetic (%)	0	25	p=0.044*
History of hypertension (%)	87	92	p=0.829
History of hyperlipidaemia (%)	27	36	p=0.167
Current smoker (%)	13	10	p=0.755
Systolic BP (mmHg)	117.8+/-23.0	138.3+/-31.8	p=0.062
Diastolic BP (mmHg)	74.0+/-12.1	77.0+/-11.9	p=0.525
Cholesterol level (mmol/L)	5.6+/-1.3	6.0+/-2.3	p=0.576
Haemoglobin (g/dL)	12.2+/-0.9	11.5+/-1.8	p=0.233

Chapter 6

Haemoglobin and Left Ventricular Abnormalities

6.1 Introduction

There are numerous observational studies evaluating the relationship between haemoglobin and abnormalities of LV structure and function in patients with CRF. Almost uniformly, these studies demonstrate that lower haemoglobin values are associated with increased LV mass and LVDil and this relationship has been observed in patients with pre-dialysis renal failure, ESRF and in those with a functioning renal allograft (23,42,69,91,97,100,110-111).

Anaemia results in several adaptive physiological responses designed to improve tissue oxygenation. Non-haemodynamic responses include an increase in erythropoietin production by the peritubular cells in the cortex-medullary border of the kidney and an increase in the intra-erythrocyte concentration of 2,3 diphospoglycerate (DPG) (262). Haemodynamic responses to anaemia are more complex and result in an increase in cardiac preload, a decrease in systemic vascular resistance leading to a decrease in cardiac afterload, all of which result in an increase in CO (99). This CV response to anaemia is appropriate and usually reversible but in patients with renal failure it has been suggested that this response becomes maladaptive and results in eccentric LVH and LV remodelling. Reasons postulated for the response becoming maladaptive include the 'hypermetabolic' state associated with CRF (263).

Despite a consistent association of anaemia with LV mass, results from prospective randomised trials such as the CHOIR and CREATE trials (107-108), designed to prove

the benefit of treatment of anaemia on mortality and via regression of LV mass, have been disappointing. Only the study of London *et al.* has shown that regression of LVH with a combined treatment approach for both hypertension and anaemia confers improved outcome in patients on RRT (75).

Confounding factors exist in observational studies which may help explain why an association between LVH and anaemia was observed. For example, it is well recognised that during an acute illness haemoglobin level will fall and may take many months to recover and inflammatory mediators may play a role in the anaemia of CRF (264). There is also an association between a higher erythropoietin dose and adverse outcome at every haematocrit level, including those over 39% (265) and it may be that anaemia is simply a marker of disease severity and therefore only indirectly associated with outcome.

Another significant confounding effect is the fact that the increased CO associated with anaemia results in an increased diameter of the LV. This in turn will result in the calculation of larger ventricular volumes and using M-mode echocardiography, a falsely higher LV mass. A direct method of measurement that is independent of loading conditions, or more accurately 'volume status-independent', is therefore attractive and may result in defining a more meaningful relationship between LV mass and anaemia. Furthermore, it may demonstrate a weaker association between ventricular mass and anaemia and help partly explain why regression of LV mass and improved outcome has not been consistently observed in studies thus far.

We therefore aimed to examine the relationship between LV mass and anaemia using a direct and relatively loading independent method of measuring LV mass, namely CMR.

6.2 Methods

6.2.1 Subjects

Patients were recruited from the West of Scotland renal transplant waiting list or directly from the renal transplant assessment clinic at the Western Infirmary, Glasgow. All patients gave informed consent and the study had approval from the local ethics committee.

6.2.2 Procedure

Patients attended on a post dialysis day for screening. The screening procedure carried out is described in Chapter 2.

6.2.3 Statistics

Statistical analysis was performed using SPSS Version 11.5 software (SPSS inc. Chicago IL, USA). Baseline data are expressed as mean +/- SD or median, if not normally distributed. Differences between the groups were assessed using a two-sample t test (normally distributed data) or Mann Whitney U test (nonparametric data). A p-value of less than 0.05 was considered significant. 95% confidence intervals for differences between groups in mean percentage change from baseline are given. Correlations between continuous values were assessed using Pearson's correlation coefficient for parametric data.

6.3 Results

6.3.1 Clinical features and baseline haemoglobin

Data on haemoglobin and LV abnormalities, as well as other screening tests, were available for 148 patients. Follow up screening with repeat CMR after at least 6 months was carried out in 84 patients and follow up data detailing LV abnormalities and haemoglobin value was available for these patients. Haemoglobin values, were available, for patients attending a regular clinic in the West of Scotland were averaged over the preceding 3 months prior to screening. Haemoglobin values ranged from 8.3g/dL-15.9g/dL with an average of 11.5g/dL and are displayed in Graph 6.1 for the whole cohort. In this cohort, 47 patients (32%) were defined as anaemic with a haemoglobin value consistently less than 11g/dL.

The cohort was split into two groups on this basis for examining the relationship between haemoglobin and LV abnormalities. The subjects in the anaemic and 'non-anaemic' groups were well matched at baseline for standard CV risk factors and baseline demographics for both groups are displayed in Table 6.1. There were no significant differences between the groups, for age (p=0.324) or sex (p=0.100) groups and no significant differences between groups in the length of renal failure (p=0.734), length of time on dialysis (p=0.785) or aetiology of renal failure (p=0.643).

With regard to medication, the patients who were anaemic were more likely to be taking aspirin (39% vs. 24%) but this difference did not reach statistical significance (p= 0.060) and there were no significant differences between the groups with regard to any medication taken including erythropoietin (p=0.953).

With regard to co-morbidity, again, there were no significant differences between the groups with regard to past medical history of IHD, other atherosclerotic disease or CHF and patients with anaemia were no more likely to have high BP (p=0.652), be a smoker (p=0.488) or have a history of diabetes (p=0.958).

In keeping with previous reports of decreased exercise tolerance in patients with anaemia in ESRF, anaemic patients performed less well during ETT, managing an average of 6.2+/-2.4 minutes compared to 7.4+/-2.4 minutes in the non-anaemic group (p=0.039). However, they were no more likely to have an abnormal or ischaemic ETT.

6.3.2 Haemoglobin and erythropoietin

Almost three quarters of the cohort (73.6%) were established on erythropoietin. There was no significant difference in haemoglobin value between the patients on erythropoietin and those not on erythropoietin (11.6 +/-1.54g/dL vs. 11.6+/-1.69g/dL, p=0.969). There was no significant difference in systolic BP between those on erythropoietin and those not on erythropoietin (135+/-25mmHg vs. 137+/-22mmHg, p=0.59) and no difference in diastolic BP (79+/-12mmHg vs. 81.3+/-11mmHg, p=0.45). Patients on erythropoietin were not prescribed a higher number of antihypertensive medications than those not on erythropoietin (1.2+/-1.1 vs. 1.5+/-1.4, p=0.23) and were not more likely to be prescribed any particular antihypertensive.

6.3.3 Haemoglobin and left ventricular abnormalities

With initial analysis involving the complete cohort, haemoglobin only correlated significantly with EDV (p=0.027, r=-0.188) (Graph 6.2). There was no correlation

between haemoglobin and LV mass (p=0.627, r=-0.042) (Graph 6.3), EF (p=0.198, r=0.110), ESV (p=0.142, r=-0.134) or stroke volume (p=0.067, r=-0.157).

Results of the differences in LV parameters between anaemic and non anaemic patients are listed in Table 6.2. The anaemic group had a significantly higher EDV compared to the non anaemic group (84.0+/-31.4 vs. 72.5+/-28.5, p=0.038) (Graph 6.4). There was a smaller non-significant difference in ESV between the groups and this relative difference resulted in a significantly higher stroke volume in the anaemic group. This was reflected in a significantly higher CO in patients with low haemoglobin values (p=0.020). This however did not translate into a difference in EF between the two groups. Notably, although there was a difference in EDV between groups, there was no difference in LV mass (Graph 6.5)

When specific LV abnormalities were examined individually, no significant differences were found between those with LV abnormalities and those with normal ventricles. Of the total cohort, 15% were found to have LVSD as defined as EF of less than 56% (33). Those with LVSD had a lower mean haemoglobin value to those with a normal LV although this did not reach statistical significance (10.9+/-1.5g/dL vs. 11.9+/-1.7g/dL, p=0.054). Turning to those patients with LVH, 70% of the cohort had LVH as defined as a LVMI of >68g/m^2 for women and >83g/m^2 for men (33). Again, there was no significant difference in haemoglobin levels between those with LVH and those without LVH (11.5+/-1.6g/dL vs. 11.9+/-1.6g/dL, p=0.169. The group of patients with LVDil was relatively small compared to previous echocardiographic studies in patients with ESRF and LVDil was not observed in isolation from other LV abnormalities. A total of 16% of the cohort had LVDil and although EDV was observed to be higher in those who were

anaemic, patients with LVDil did not have a significantly lower haemoglobin value compared to those with a normal LV (11.2+/-1.8 vs. 11.9+/-1.7, p=0.149)

6.3.4 Haemoglobin and the development of left ventricular abnormalities

As discussed in Chapter 5, 84 patients had two CMR scans more than six months apart. No significant changes were observed across the cohort with regard to progression of LV volumes or function but a significant number of patients with initially normal ventricles progressed to develop concentric LVH. When these patients were compared to those whose ventricles remained normal no difference in haemoglobin value was found (11.5+/-1.8g/dL vs. 12.1+/-0.8g/dL, p=0.233) between groups.

6.4 Discussion

The physiological response mechanisms of the body to anaemia include increased venous return to the heart, an increased heart rate and a resultant increase in CO (99). An increase in CO has been confirmed indirectly in several studies in patients with renal anaemia and it has been shown that an increase in haematocrit from 20% at baseline to 31% after epoetin treatment is associated with a reduction in CO from 4.4L/min to 3.4L.min (266). CO is the product of heart rate and stroke volume of the heart and in normal physiological circumstances stroke volume depends on EDV. This is known as the Frank-Starling mechanism which states that the 'output of the heart is determined by the amount of blood flowing into the heart'. In this study, patients with a low haemoglobin value were found to have a significantly higher CO compared to those with higher haemoglobin concentrations. This was due to mainly an higher EDV with a relatively preserved ESV and resultant higher stroke volume in patients with lower haemoglobin values. There was no difference in heart rate between the two groups. EF was not significantly different as EDV was not elevated sufficiently in comparison to ESV to alter the value of calculation of EF= EDV-ESV/EDV significantly.

In patients with normal renal function the majority of the CV responses to anaemia, such as vasodilatation and increased CO are adaptive and reversible. However, in patients with CRF it has been postulated that the normal physiological adaptive processes become maladaptive, and this results in stimulation of LVH via eccentric remodelling (110). Once established, echocardiographic evidence suggests this LVH is not reversible and contributes to the increased mortality observed in this population. Although we found anaemic patients to have higher circulating volumes than those with haemoglobin values

above 11g/dL, we did not find any associated difference in LV mass between the two groups. This finding may reflect the fact that this cohort of patients had relatively high haemoglobin values compared to previous observational studies or the relatively small proportion of patients in this cohort with eccentric LVH in comparison to concentric LVH. However, it may also reflect the fact that when measurements of LV diameter are not used in the calculation of LV mass, as is the case with M-mode echocardiography, LV mass is not as strongly associated with haemoglobin values as previously thought. This lack of association between LV mass and haemoglobin values has also been shown in a previous CMR study by our group in a cohort of 35 patients on RRT (202) but is in contrast to another study by our group in 44 patients on haemodialysis where CMR measurements of LV mass did showed a weak negative correlation with haemoglobin (267).

When haemoglobin values in patients with individual LV abnormalities were examined in comparison to haemoglobin values in those with normal ventricles, no significant differences were found for any specific LV abnormality. Mean haemoglobin values were lower in those patients with LV abnormalities, most marked in those with LVSD, but these differences did not reach statistical significance. This again is in contrast to previous echocardiographic studies but again may reflect a fitter population or a population with a low prevalence of eccentric LVH.

The fact that patients with anaemia in this cohort had a significantly increased CO compared to those with a haemoglobin concentration of >11g/dL but no significant difference in BP suggest those with anaemia have a relatively lower systemic vascular resistance (SVR=MAP/CO). This is a usual physiological response to anaemia of hypoxic

dilatation (99). Studies of anaemic renal patients have shown a decrease in forearm blood flow and a marked increase in SVR in response to oxygen supplementation and it has been suggested that an exaggerated increase in SVR in response to erythropoietin administration is partly responsible for the rise in BP observed in 30% patients (268). The increase in SVR and blood viscosity associated with reversal of anaemia would usually result in release of nitric oxide from the vascular endothelium causing vascular relaxation and antithrombotic effects but it has been observed in hypertensive patients that nitric oxide mediated endothelial function is impaired (269) and it is thought that these mechanisms may help explain the adverse outcome in the treatment arms of trials targeting anaemia especially those trials aiming for a high haemoglobin value in patients with CRF (107,116).

The dominant ventricular abnormality in this cohort is concentric LVH and putting the arguments of methods of measurement aside, it is interesting that the prevalence of concentric LVH is so high in all studies of patients with ESRF given the substantial volume overload. It is well documented that anaemia is associated with adverse CV morbidity and mortality in this population (100-101) and this could partly be explained by the combination of a stiff hypertrophied LV and an increase in CO. The increase of myocardial thickness and associated fibrosis that ensues leads to a non-compliant ventricle poorly able to accommodate an increased venous return. This further increases already high end-diastolic pressure thereby increasing cardiac work and myocardial oxygen demand and potentially inducing ischaemia and arrhythmias.

In addition to adverse outcome several studies have reported that anaemic patients with ESRF perform less well during exercise than those who are not anaemic (104). In keeping

with this finding, of the 120 patients (80%) in our study who underwent ETT, those who were anaemic only managed 80% of the total exercise time that those with a haemoglobin concentration of >11g/dL achieved, although it should be remembered that anaemia is associated with other chronic conditions which could influence exercise tolerance.

The lack of association between anaemia and LVH in patients who have been established on RRT for several years could potentially be explained by the fact that any effect of anaemia on the LV may have already have taken place. We therefore examined the relationship between the development of new LVH and anaemia. Although the numbers were small (13 patients), we found no significant difference in mean haemoglobin value between those who developed LVH and those in whom ventricular anatomy remained normal. This is in contrast to previous echocardiographic studies that have suggested that degree of anaemia and a progressive decline in haemoglobin level are associated with progressive LVDil and hypertrophy in the form of eccentric LVH (69-70).

The relationship between anaemia and LV abnormalities, especially LVH, remains unclear. Anaemia is an almost universal finding in patients with ESRF, as is LVH and both are associated with an adverse outcome. The fact that controversy regarding the favourable impact of the treatment of anaemia with regard to mortaltiy still remains almost 20 years after the introduction of erythropoietin is shocking. It may be that part of the explanation for this may lie with the inaccuracy in the currently used methods of measuring LV mass and volumes and the inability of these methods to be 'volume loading-independent' in a volume loaded setting, exacerbated further by anaemia. It may be that using M-mode echocardiography has led to anaemia incorrectly being associated with LV mass in the first place or alternatively failing to identify a true impact of the

treatment of anaemia on LVMI. Combining observations of both the failure of treatment of anaemia to regress LVH and the lack of improvement in outcome in apparently adequately powered studies makes the former statement the more likely and the results of this study would support that hypothesis. Using the relatively load independent technique of CMR, with direct measurement of LV mass and volumes we did not demonstrate a relationship between anaemia and LV mass, although anaemic patients had a physiologically appropriate higher CO. Further studies are required to confirm these initial findings but we suggest that targeting regression of LVMI, measured by M-mode echocardiography, as an end-point in trials of the treatment of anaemia in patients with ESRF is questionable.

Graph 6.1 Distribution of haemoglobin levels for whole cohort. N=148

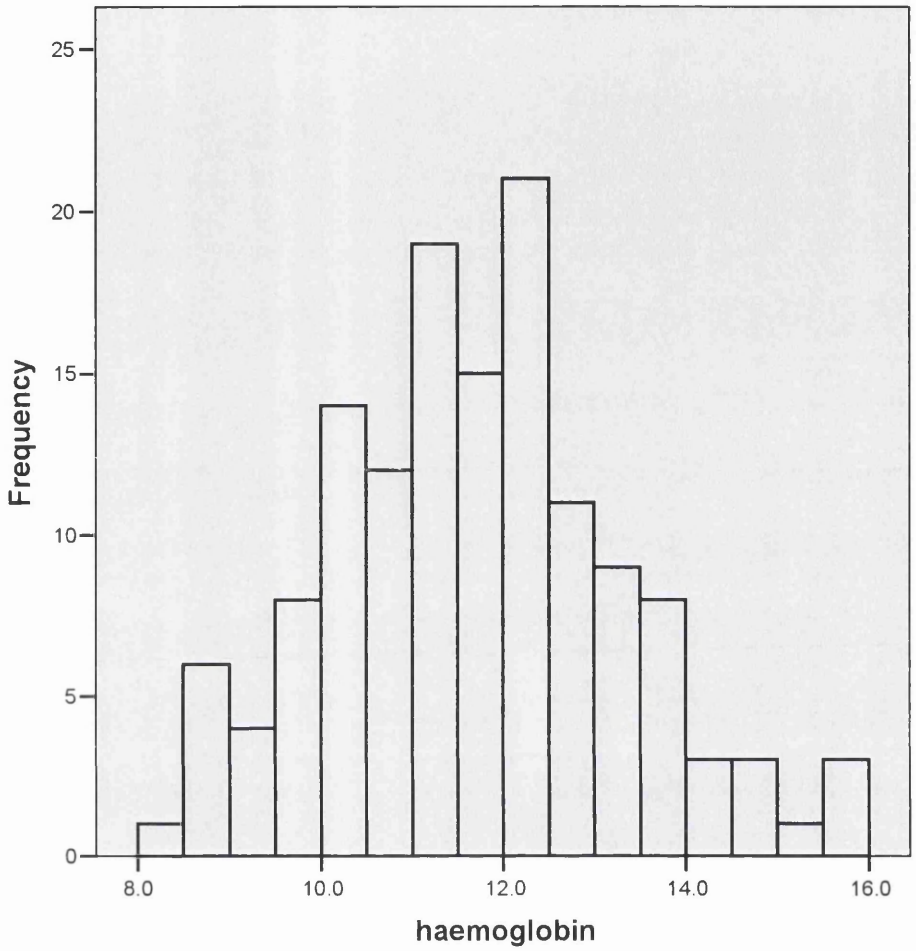
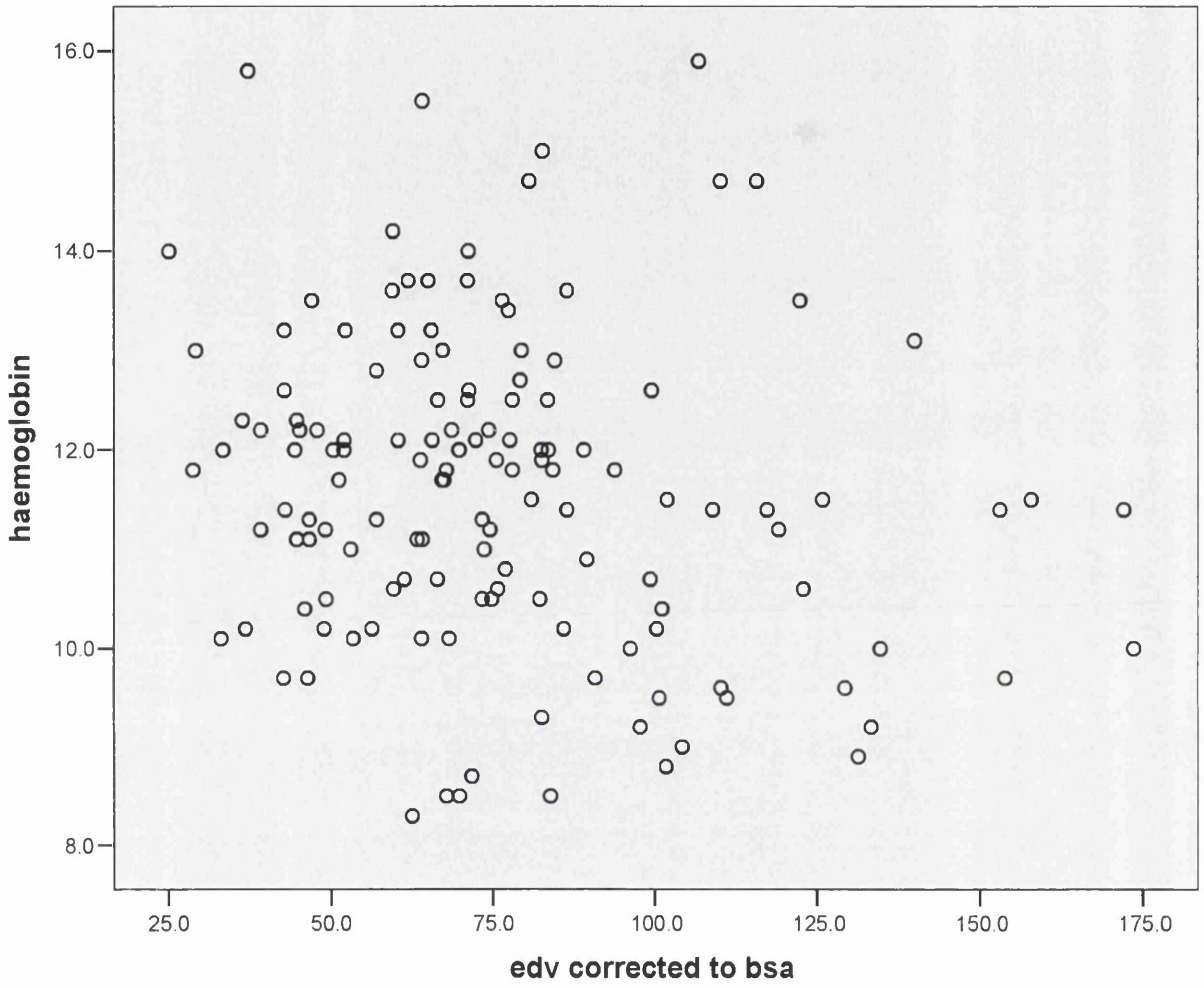


Table 6.1 Differences in baseline characteristics between anaemic and non-anaemic patients

Variable	*Anaemic Hb<11g/dL n=47*	*Non-anaemic Hb>11g/dL n=101*	*p value*
Age (years)	51.3+/-10.3	49.5+/-10.3	p=0.324
Sex (%men)	57	71	p=0.100
Duration of RRT (months)	27.2+/-24.7	34.8+/-31.6	p=0.785
Systolic BP (mmHg)	140.3+/-24.6	132.6+/-23.1	p=0.079
Diastolic BP (mmHg)	80.5+/-11.2	79.5+/-12.6	p=0.652
PMH of IHD (%)	19.1	17.8	p=0.844
PMH of Diabetes (%)	17	17	p=0.958
PMH of CHF (%)	6.4	8.9	p=0.610
Smokers (%)	34	28	p=0.488
No. of HBP drugs	1.2	1.1	p=0.875
On erythropoietin (%)	72	72	p=0.953
On aspirin (%)	39	24	p=0.060

Graph 6.2 Scatterplot demonstrating correlation between haemoglobin level and EDV for total cohort (p=0.027, r=-0.188)



Graph 6.3 Scatterplot demonstrating correlation between haemoglobin level and LVMI for total cohort (p=0.627, r=-0.042)

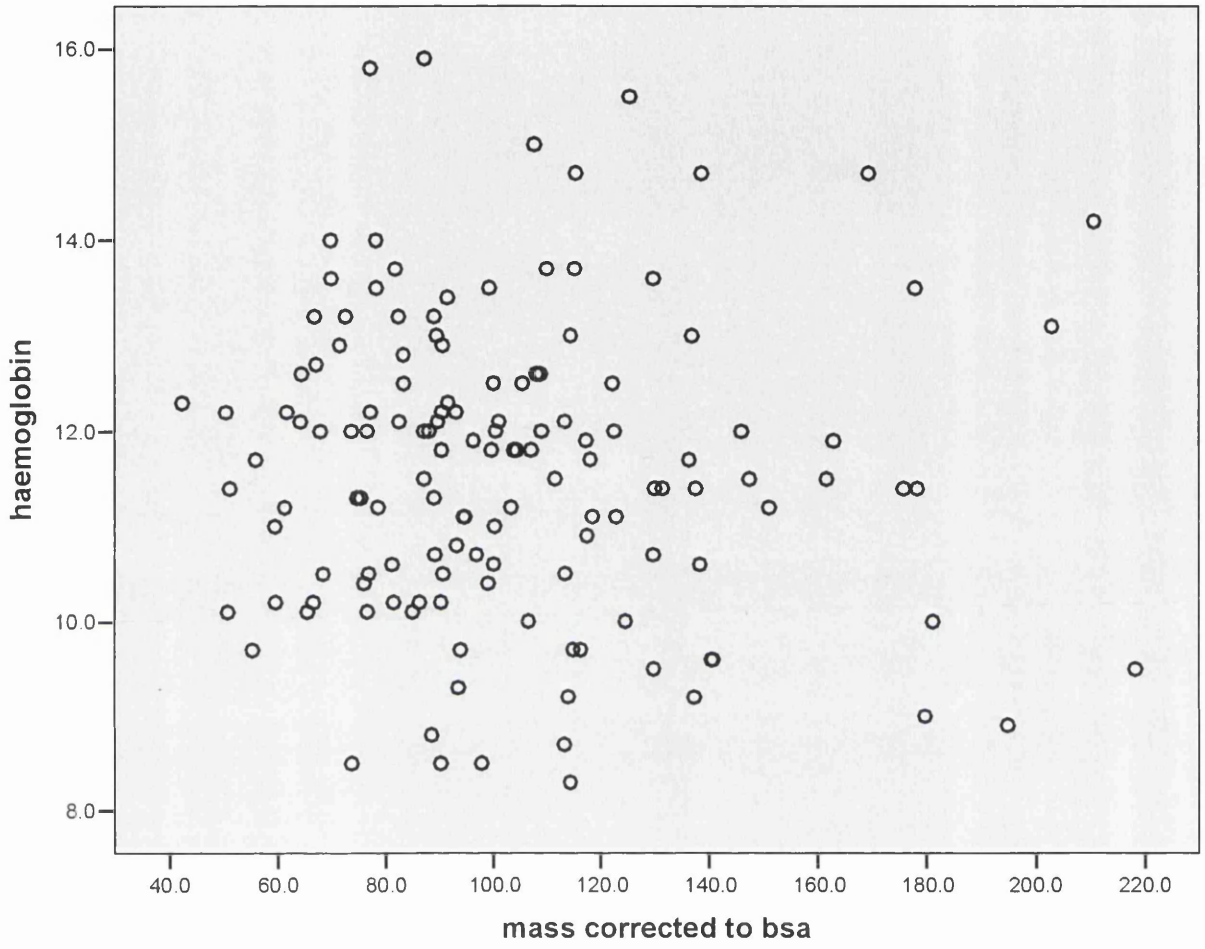


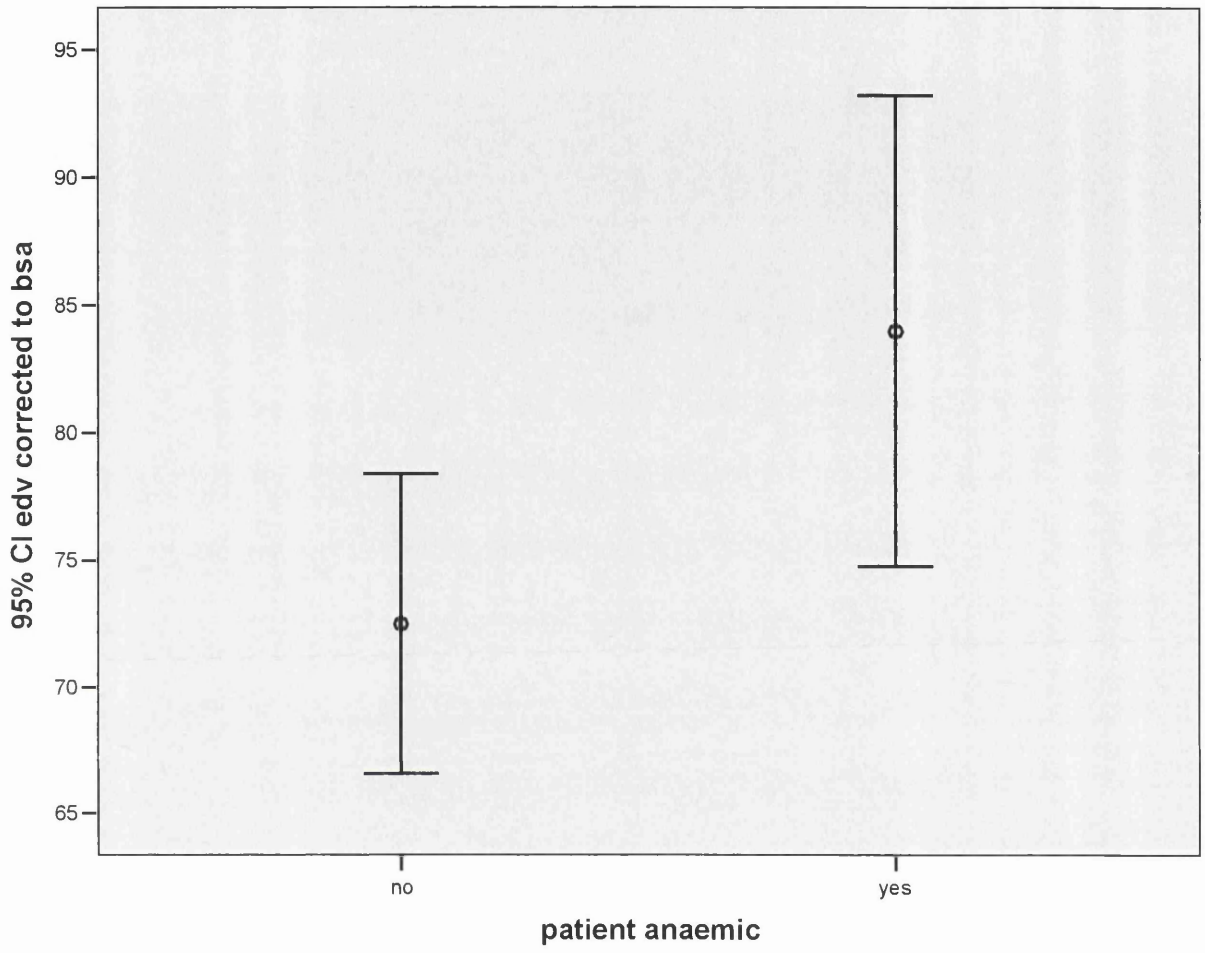
Table 6.2 Differences in LV parameters between anaemic and non-anaemic patients

Variable	*Anaemic Hb<11.0g/dL n=47*	*Non-anaemic Hb>11.0g/dL n=101*	*p value*
Ejection fraction (%)	64.9+/-12.1	65.9+/-12.9	p=0.646
End-diastolic volume * (ml/m^2)	84.0+/-31.4	72.5+/-28.5	p=0.038**
End-systolic volume *(ml/m^2)	52.3+/-21.0	45.4+/-23.6	p=0.607
Stroke volume (mls/m^2)	52.3+/-17.3	45.4+/-15.0	p=0.022**
Cardiac Output (L/min)	7.1+/-2.4	6.1+/-2.1	p=0.020**
LV mass * (g/m^2)	104.5+/-36.1	103.2+/-33.8	p=0.836
Heart Rate (beats per min)	75+/-14	74+/-15	p=0.815)

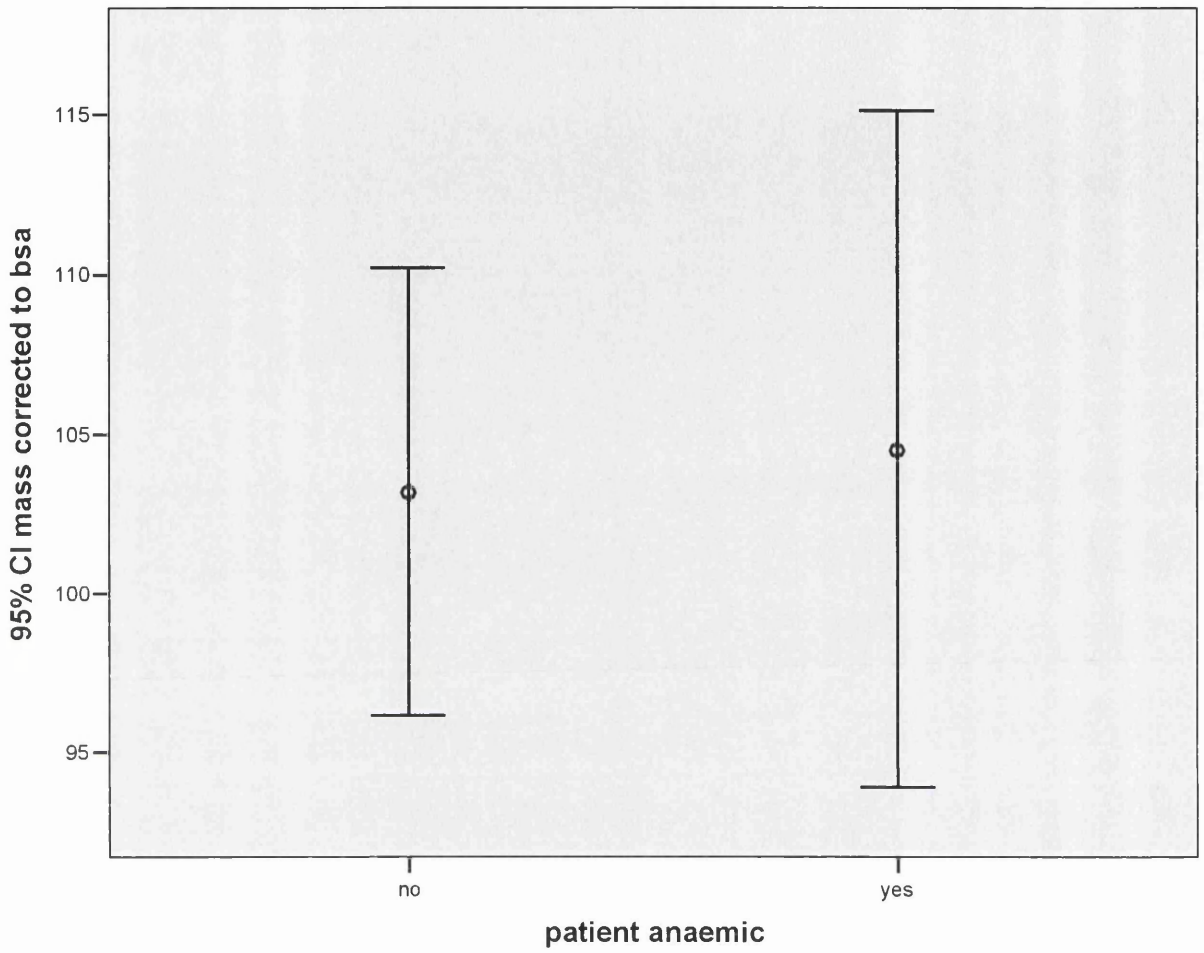
*corrected to BSA

**significant result at $p<0.05$.

Graph 6.4 Difference in EDV between anaemic and non-anaemic patients (p=0.038)



Graph 6.5 Difference in LVMI between anaemic and non-anaemic patients (p=0.836)



Chapter 7

Brain Natriuretic Peptide and Left Ventricular Abnormalities

7.1 Introduction

The diagnostic, prognostic, screening and therapeutic monitoring roles of natriuretic peptides in CVD continue to expand and with the introduction of nesiritide in the US, a recombinant form of human BNP, natriuretic peptides may also have a therapeutic role in CHF themselves (270). The original and probably still the most robust use of serum BNP, is for the diagnosis of LVSD in patients from the normal population presenting with breathlessness or other symptoms suggestive of heart failure and due to the high NPV of BNP, a diagnosis of LVSD can be reliably excluded in a breathless patient with a low BNP value (122-123).

Patients with ESRF have a high prevalence of symptoms suggestive of CHF such as breathlessness and ankle oedema and previous studies have shown that the prevalence of CHF in patients commencing RRT is as high as 40% (14). Assessing the diagnostic utility of BNP for the diagnosis of LVSD or other structural abnormalities in the context of ESRF is fraught with difficulties but despite these problems, several studies have found that BNP has a potentially diagnostic role for patients with uraemic cardiomyopathy. However in contrast to studies in the normal population, BNP seems to correlate more strongly with LVMI than EF in patients with ESRF.

In a study of 246 patients on RRT (86% on haemodialysis) by Mallimaci *et al.* (139), serum BNP level was found to detect echocardiographically determined LVH with a

sensitivity of 88% and a PPV of 87% but with a disappointingly low NPV of 31%. The corresponding values for the detection of LVSD included a sensitivity of 94% and a high NPV of 96% but the PPV was very low at 15%. Other studies have shown similar findings and in the study of Nishikimi T *et al.* (138), the additional influence of CAD was assessed and patients with LV abnormalities and CAD had higher levels of BNP than those with LV abnormalities and no CAD.

The reasons for a stronger correlation of BNP with LVMI in these studies are unclear but it may be partly explained by the confounding effect of a higher prevalence of CAD in patients with LVSD compared to those with concentric LVH. Furthermore, many of these studies have excluded patients with known IHD and therefore the group of patients with LVSD are small. However, if BNP is going to be considered as a potential diagnostic tool for patients undergoing assessment for renal transplantation, it needs to be sensitive and specific enough to reliably identify uraemic cardiomyopathy in any patient considered for transplantation.

Biomarkers such as natriuretic peptides are easily measured, can predict outcome in patients undergoing cardiac transplant and reliably exclude LVSD in patients in the general population. A similar tool in the assessment of patients assessed for renal transplant would therefore be invaluable. Previous studies in patients with ESRF have been carried out using echocardiography and CMR imaging is now the established standard of reference for the measurement of LV abnormalities. We hypothesized that serum BNP levels may correlate more strongly with CMR measurements of LV structure and function than previous echocardiographic studies, thus improving the sensitivity, specificity and overall accuracy of BNP to detect LV abnormalities in this population.

7.2 Methods

7.2.1 Subjects

Patients were recruited from the West of Scotland renal transplant waiting list or directly from the renal transplant assessment clinic at the Western Infirmary, Glasgow. All patients gave informed consent and the study had approval from the local ethics committee.

7.2.2 Procedure

Patients attended on a post dialysis day for screening. The screening procedure described in Chapter 2 was carried out for each patient.

7.2.3 Statistics

Statistical analysis was performed using SPSS Version 11.5 software (SPSS inc. Chicago IL, USA). Results are expressed as mean with standard deviation for normally distributed data. Correlations between continuous values were assessed using Pearson's correlation coefficient for parametric data. Comparisons between groups were made by the student's T test for normally distributed and the Wilcoxon rank-sums tests for non-normally distributed data. Logarithmic transformation was used for BNP levels due to skewed distribution. The determinants of BNP levels were investigated by multivariate regression analysis using a stepwise paradigm.

7.3 Results

7.3.1 Baseline demographics of cohort

Data on BNP level and LV abnormalities measured using CMR imaging as well as other screening tests were available for 126 patients. Baseline demographics were similar to that of the total initial cohort (Table 3.1) and there were no significant differences between the BNP cohort and the total cohort with regard to baseline demographics. Age range of the BNP cohort was 26-70 with a mean age of 51 (+/-9.8) years old and 83 patients in the cohort (66%) were men. Average length of renal failure was 8.3 years with a range of 0.5-15 years and patients had been on dialysis for an average of 2.8 years with a range of 0.5-12 years. A higher proportion of patients were established on haemodialysis (60%) with the rest established on PD. Of the patients established on haemodialysis, 20% were using overnight or 'long time' dialysis and of the patients established on PD, 62% were using CAPD and the rest APD. Almost one fifth (19%) of the cohort had undergone previous renal transplantation.

7.3.2 Left ventricular abnormalities

Normal ranges for LV abnormalities measured using CMR are shown in Table 4.1. At baseline screening, the average EF of the cohort was 65% (+/-12.7%) with a range of 16-85%. In the BNP cohort, 19 patients (15%) had LVSD defined as an EF of <56% measured by CMR imaging. Average LV mass corrected to BSA was 113.8g/m^2 (+/-34.5g/m^2) for men and 86.7g/m^2 (+/-26.2g/m^2) for women. The majority of patients (71%) had elevated LV mass. Average EDV corrected to BSA and ESV corrected to BSA were 81.8ml/m^2 (+/-31.6ml/m^2) and 30.4ml/m^2 (+/-23.6ml/m^2) respectively for men and

68.9ml/m^2 (+/-28.5ml/m^2) and 22.8ml/m^2 (+/-22.1ml/m^2) respectively for women. 22 patients (17%) had a dilated ventricle. Just over one quarter of the cohort (28%) had a normal ventricle defined by CMR imaging and 16 patients (13%) had all three LV abnormalities of 'uraemic cardiomyopathy'. All patients with LVSD had an elevated ventricular mass and a dilated ventricle. Thus this BNP cohort had no significnat differences with regard to LV parameters compared to the total initial cohort (Table 4.2).

7.3.3 Standard cardiovascular risk factors.

Mean systolic BP was 135mmHg (+/-22.3mmHg) and mean diastolic BP was 80mmHg (+/- 11.1mmHg). The majority (95%) of patients had a history of hypertension. There was a history of IHD in 16.7% (21 patients) of the cohort and 8.7% had sustained a previous AMI (11 patients).There was a family history of premature IHD in 28%. Diabetes was present in 15.9% (20 patients) of the cohort and 33.3% of patients had a previous history of hyperlipidaemia. With regard to smoking, 28.8% of patients were current smokers and a further 26.4% were ex-smokers.

7.3.4 Drug therapy.

At baseline screening, 70% of the cohort was receiving erythropoietin regularly. Two-thirds of patients were on at least one anti-hypertensive medication with 30.6% on a single medication for hypertension, 16.1% on dual antihypertensive medication with 17.7% and 2.2% of patients on three and four anti-hypertensives respectively. Beta-blockers were used as an anti-hypertensive medication in 33.2% of patients and ACEI in

21.1%. A significant proportion of patients were on oral diuretics (32.2%) and 28.8% patients were on a statin.

7.3.6 BNP and baseline left ventricular abnormalities.

Initially the relationship between BNP level and baseline LV abnormalities for the whole cohort was examined. As BNP has a skewed distribution logarithmic transformation was performed prior to analysis. For the total cohort, mean serum BNP was 127pmol/L with a range of 0-2093pmol/L. There were significant correlations between serum BNP levels and all LV measurements and these are illustrated in Graphs 7.1-7.4. The strongest correlation between BNP and LV abnormalities was with LVMI ($p<0.001$, $r=0.585$). Thereafter, BNP also correlated positively with EDV corrected to BSA ($p<0.001$, $r=0.430$) and ESV corrected to BSA ($p<0.001$, $r=0.487$) and negatively with EF ($p<0.001$, $r=-0.455$).

7.3.7 Usefulness of BNP to detect left ventricular abnormalities.

Initially the cohort was split into two groups for analysis based on the finding of an abnormal LV. Those with a normal ventricle defined by CMR imaging were the 'control group' and those with an abnormal LV defined by CMR were then examined in comparison to the 'control' group to examine the diagnostic potential of BNP with regard to identifying patients with an abnormal LV.

Patients with an abnormal ventricle had a significantly higher BNP level when compared to those with a normal ventricle (26pmol/L+/-66.1pmol/L vs. 166.6pmol/L+/-367pmol/L, $p=0.002$). The significant baseline differences between the two groups are shown in

Table 7.1 and differences in LV abnormalities between the two groups are shown in Table 7.2. Those with an abnormal LV had a significantly higher systolic BP (p=0.023), were more likely to be on haemodialysis (p=0.001) and have a history of diabetes (p=0.029). Patients with an abnormal LV were no more likely to be on an ACE inhibitor, beta-blocker or diuretic than those with a normal LV.

Initially, a range of BNP values were trialled to identify which level of BNP was the most accurate upper limit of 'normal' for the cohort. An upper limit of 20picomol/L gave the best sensitivity, specificity and overall accuracy through the group values and this was used to define 'normal' and 'high' levels for BNP in the cohort. This is higher than the level in the normal population of a cut-off of 5.2picomol/L (35). The sensitivity of BNP to detect any abnormality was 65% and the specificity 79%. This gave a PPV for BNP to detect any LV abnormality of 88% and a NPV value of 59%. The ROC curve is shown in Graph 7.5 with an area under the curve of 0.707.

7.3.8 BNP and left ventricular hypertrophy.

Patients with concentric LVH, measured using CMR imaging, were compared with the group of patients with a normal LV to examine the potential utility of BNP to identify patients with ESRF who have concentric LVH. BNP level was significantly higher in the group of patients with LVH when compared to those with normal ventricles (26pmol/L+/-66.1pmol/L vs. 175pmol/L+/-157pmol/L, p=0.030). The sensitivity of BNP to detect LVH was 63% and the specificity 79%. The PPV of BNP to detect LVH was 79% and the NPV 60% (Table7.3). The ROC curve is shown in Graph 7.6 with an area under the curve of 0.739.

7.3.9 BNP and left ventricular dilation.

There were 22 patients in the cohort with a dilated left ventricle (LVDil). This group was compared with the 33 patients in the cohort with a normal LV with regard to BNP levels and the utility of BNP to detect LVDil. BNP levels were significantly higher in the group with LVDil than those with a normal LV (16pmol/L+/-30.1pmol/L vs. 599pmol/L+/-122.3pmol/L) p=0.001. The sensitivity of BNP to detect LVDil was 68% with a specificity of 79%. The PPV of BNP to detect LVDil was 68% and the NPV of a high BNP ruling out LVDil was 80% (Table 7.3). The area under the ROC curve was 0.767.

7.3.10 BNP and left ventricular systolic dysfunction.

Finally, the group of patients with LVSD were compared to the group with a normal LV. BNP level in the group was significantly higher in those with LVSD than in those with a normal ventricle (16+/-30pmol/L vs. 395+/-534pmol/L, $p<0.001$). The sensitivity of BNP to detect LVSD was 74% and the specificity 79%. The PPV of BNP to detect LVSD was 67% with a NPV of 90% (Table 7.3). The ROC curve is shown in Graph 7.8 and area under the curve is 0.811.

7.3.11 Determinants of BNP in patients awaiting renal transplantation.

The whole cohort was examined using lgBNP as the outcome variable and the set of initial independent variables used in a multivariate linear regression model were LVMI, EDV corrected to BSA, EF, age, sex, systolic and diastolic BP, length of renal failure, mode of RRT, a history of CHF, IHD or diabetes and haemoglobin. These variables were

then used in a backward elimination strategy to identify independent determinants of BNP. Table 7.4 shows univariate and the independent predictors of BNP.

All parameters of LV mass, volumes and EF were significant on univariate testing as were systolic BP and a history of diabetes. Interestingly, type of dialysis therapy was not significant on univariate analysis nor was length of renal failure or length of time on dialysis.

The only independent predictors of BNP found in the regression model were LVMI ($p<0.001$, $\beta=0.435$) and EF ($p=0.043$, $\beta=-0.171$). A history of IHD or measures of LV volume were not found to be independently associated with BNP level.

7.4 Discussion

Patients with renal failure, especially those who have ESRF have a high mortality rate mainly attributable to CVD. In this population the major predictors of mortality are structural LV abnormalities, especially LVSD. A significant proportion of patients with ESRF will be considered as potential candidates for renal transplantation and part of the assessment should include cardiac risk stratification. Many of these patients will undergo echocardiography for assessment of LV abnormalities but waiting times in some centres are still long and measurements made often depend on timing of the study in relation to dialysis cycle (195) and outwith the setting of clinical trails, a hospital appointment for an echocardiogram will not often fall at the optimum time of 4-6 hours post dialysis session. Furthermore, echocardiographic images are often sub-optimal due to poor echo windows in as many as 40% of adult patients (186).

A screening test such a BNP, that could be carried out at the transplant assessment clinic, would therefore be attractive in this population to enable identification of patients with LV abnormalities and prompt further plans for cardiac investigation at that time. Previous studies have suggested that natriuretic peptides may be useful in this population but that other factors such as drug therapy and methods of excretion may affect the accuracy of cardiac biomarkers such as BNP in patients with renal disease (132-133,136,138).

At time of writing, this is the first study examining the relationship of the natriuretic peptide BNP and LV abnormalities in a group of patients with ESRF using CMR as the method of measurement of LV abnormalities and several of our findings were similar to previous echocardiographic studies. As in the study of Nakatini *et al.* (148) we also found that BNP level was significantly higher in patients on haemodialysis compared to those

on CAPD. In our BNP cohort there were no significant differences in prevalence of IHD between patients on differing forms of RRT and several explanations exist for the higher observed level of BNP in patients on haemodialysis. Nakatini *et al.* proposed that the higher haemodynamic burden on patients of haemodialysis could account for higher circulating levels of BNP. However, type of dialysis therapy was not found to be a determinant of BNP level in this study and therefore does not support this hypothesis. Alternatively, patients on CAPD tend to have greater residual renal function than those on haemodialysis and lower BNP levels in patients on CAPD may reflect greater clearance. In our cohort, patients on haemodialysis had a higher prevalence of LV abnormalities (Table 7.1), mainly in the form of LVH, compared to those on CAPD and it is likely that selection bias in choosing mode of RRT plays a major role in the higher circulating levels of BNP in patients on haemodialysis.

Using CMR, serum BNP levels correlated strongly with all LV measurements; positively with mass and volumes and negatively with systolic function and similar to previous echocardiographic studies, BNP correlated most strongly with LV mass. In the study of Mallamacci *et al.* (140), patients with known CHF were excluded and 13% of patients in their cohort were found to have LVSD whilst 79% had LVH. In our cohort there was a slightly lower prevalence of LVH (71%) and a similar prevalence of LVSD (15%) and we found a stronger correlation of BNP measurements with LVMI and LV volumes than was observed in the study of Mallamacci *et al.* Whilst correlation with LV wall thickness was strong in the study of Mallamacci *et al.* ($r=0.5$, $p<0.001$) the correlation with LV volumes was not, only just reaching statistical significance ($r=0.12$, $p=0.05$). In our study using CMR we found a stronger correlation of BNP with mass and volumes (Graph 7.1-

7.3 and a similar correlation of BNP with EF (Graph 7.4) than the echocardiographic study. Whilst it should be remembered the population of patients were different (patients on RRT without CHF vs. patients on RRT suitable for transplant), it is tempting to speculate that the better correlation of BNP with LV measurements is this study is due the improve accuracy of the imaging technique used.

Why LVH is consistently shown to have a stronger relationship with BNP than LVSD in patients with ESRF is unclear. It may be that, as we have demonstrated in Chapter 4, LVSD and LVDil develop due to underlying CAD which acts as a confounder in analysis and patients with IHD were not excluded from either our study or the study of Malamacci *et al.* Also, patients with LVSD may be more likely to be established on medications such as beta-blockers and ACEI which may affect BNP levels. Finally, if the development of LVH via concentric LVH is the dominant evolutionary pattern in this population and additionally is present in the majority of those with LVSD then LVH may simply play a more dominant role in triggering the production of BNP, due to the increased filling pressures required for adequate filling of a stiff hypertrophied heart, than other LV abnormalities.

In the general population it has been found that serum BNP has a sensitivity of 77% and specificity of 87% for detecting LV dysfunction (122). Its major benefit in screening for LVSD is a high NPV of 93-95% (122,271-272) meaning that a low level of BNP virtually rules out a diagnosis of LVSD. Similarly the NPV of BNP for detecting LVSD in patients presenting with breathlessness is around 98% (123,272). However, the PPV is not as high. This means that where a high level of BNP suggests a diagnosis of LVSD, other pathological conditions such as liver failure, renal failure, pulmonary conditions and

hyperthyroidism also elevate BNP levels (271). A high level of BNP therefore warrants further investigation for underlying disease but does not necessarily mean the diagnosis will be that of LVSD.

In this study we found a good NPV of BNP for excluding LVSD at 90%. However, the NPV was not high when examining the usefulness of BNP to detect any LV abnormality (59%) or concentric LVH (60%), although the PPV of BNP to detect an abnormal ventricle or concentric LVH was 88% and 79% respectively. This would suggest that although lower levels of BNP can help identify patients who do not have the higher risk abnormalities of LVDil or LVSD, it is not so valuable in excluding patients with isolated LVH or separating those with normal ventricles from those with abnormal ventricles. This is not an entirely unexpected finding as the NPV of a test will decrease as the pre-test probability of the condition being tested increases. The pre-test probability of patients with ESRF having an abnormal ventricle or concentric LVH is much higher than the pre-test probability of having eccentric LVH or LVSD. What is suggested, is that the NPV for the patients at highest risk of death is over 90%. It should also be noted that despite the lower sensitivity, specificity and predictive values found, compared to those in the normal population, the sensitivity and specificity of BNP to detect LV abnormalities is much higher than the corresponding sensitivity (31%) and specificity (81%) of the ECG to detect LV abnormalities detailed in Chapter 4 and compared to previous echocardiographic studies show a an improved combined sensitivity and specificity for the detection of both LVH and LVSD.

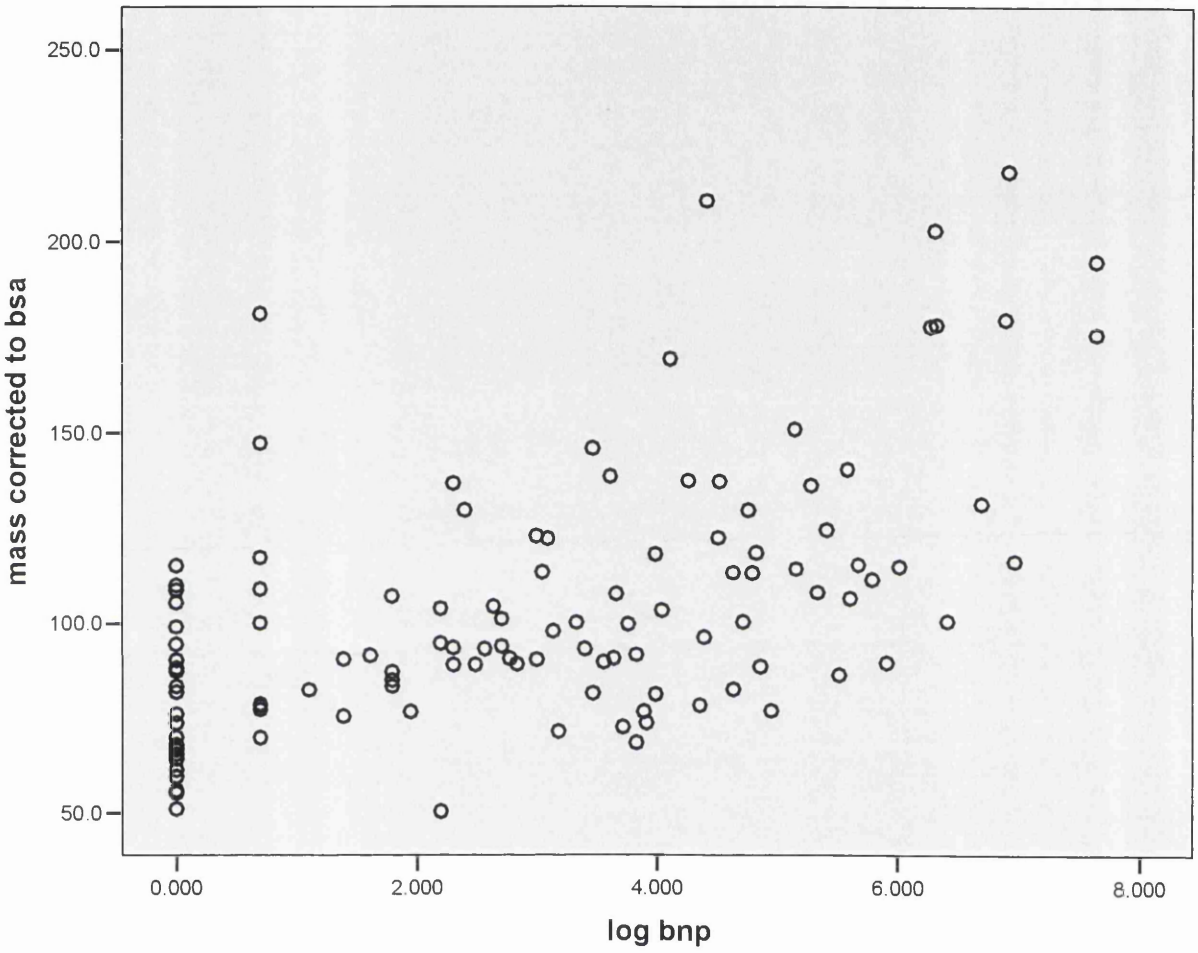
In this study only LV mass index and EF were found to be an independent predictors of BNP level. There did not seem to be any influence on BNP levels of age or sex and it

may be that the confounding effect of renal failure on circulating BNP levels means that the age and sex differences observed in the normal population are not applicable to patients with ESRF and this finding has been observed in other studies assessing the use of BNP in patients on RRT (139).

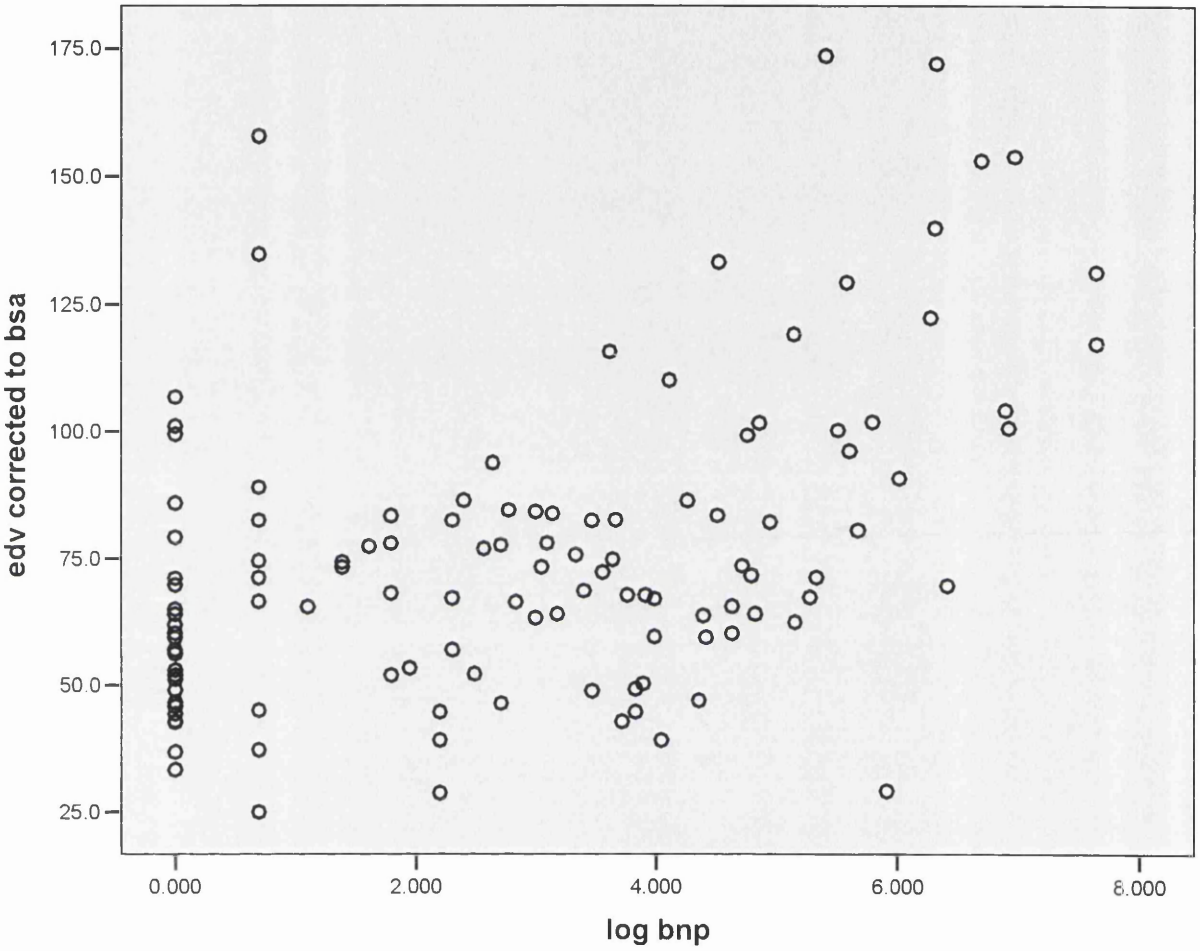
In this study we found that BNP correlated strongly and significantly with all LV parameters, measured using CMR, in patients with ESRF considered candidates for renal transplantation. Furthermore the correlation was stronger than that observed in previous echocardiographic studies. The NPV for excluding patients with all three LV abnormalities was high, suggesting a low BNP may help exclude those at greatest risk of death on the transplant waiting list. In this population the only independent determinants of BNP level were LVMI and EF.

Further studies are required in a larger group of patients, especially those with a combination of ESRF and LVSD, to confirm these findings and better establish the relationship of BNP to LVSD in similar populations. However, these findings suggest that measurement of serum BNP in patients with ESRF being assessed for renal transplant may be a useful addition to current practice to exclude those at highest risk and identify those in whom further investigation is required.

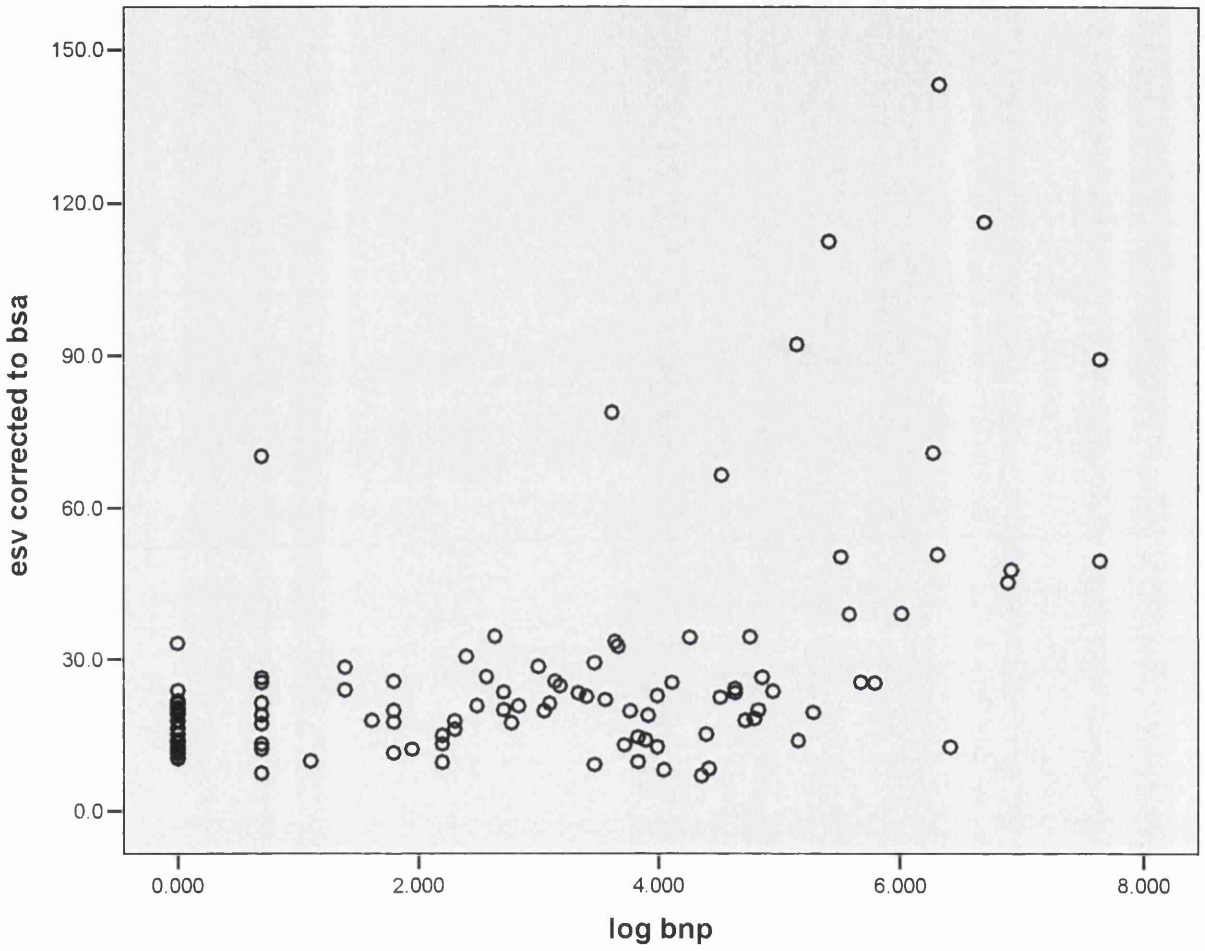
Graph 7.1 Scatterplot demonstrating correlation between log-transformed BNP and LVMI defined by CMR imaging ($p<0.001$, $r=0.585$)



Graph 7.2 Scatterplot demonstrating correlation between log-transformed BNP and EDV defined by CMR imaging ($p<0.001$, $r=0.430$)



Graph 7.3 Scatterplot demonstrating correlation between log-transformed BNP and ESV defined by CMR imaging ($p<0.001$, $r=0.487$)



Graph 7.4 Scatterplot demonstrating correlation between log-transformed BNP and EF defined by CMR imaging ($p<0.001$, $r=-0.455$)

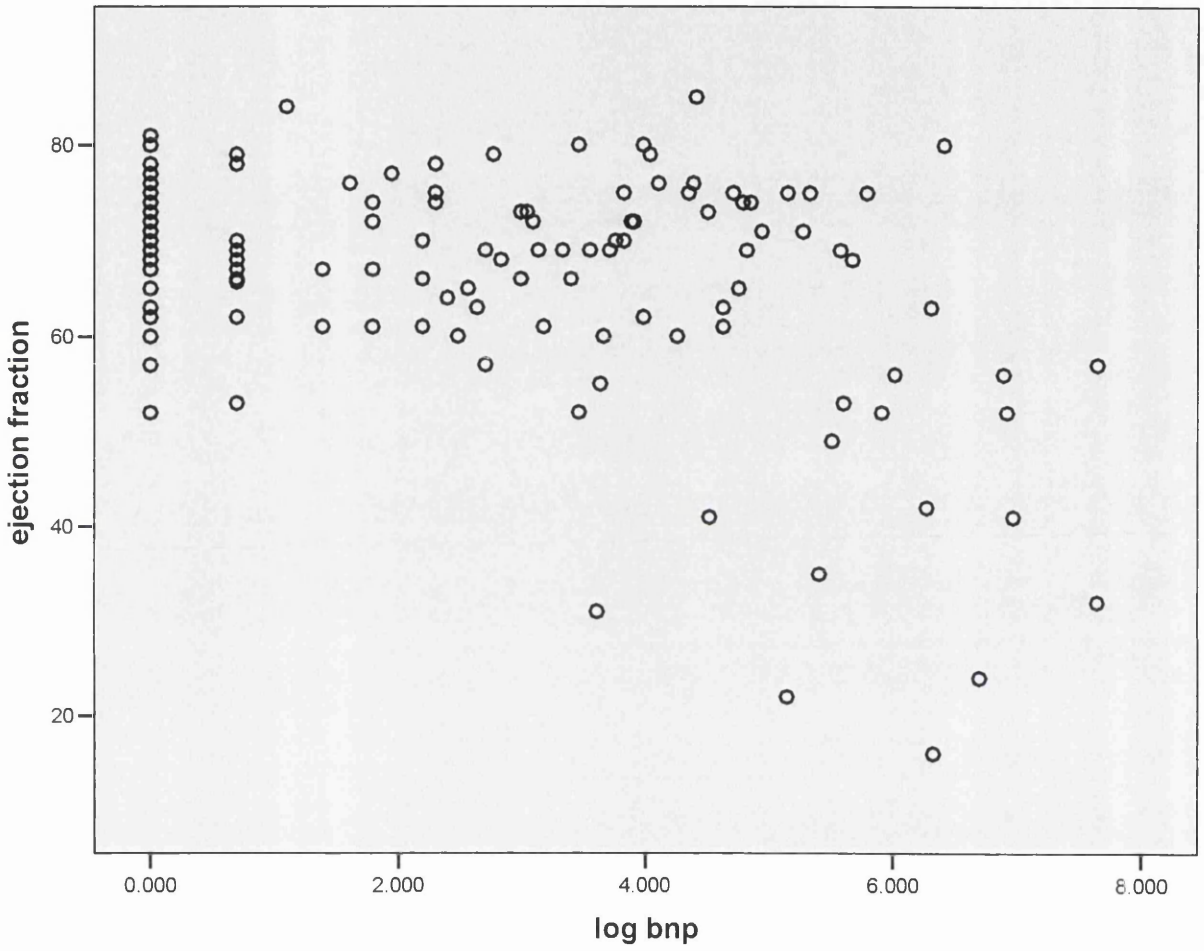


Table 7.1 Baseline characteristics and standard CV risk factors for cohort of patients in which BNP measurements available

Variable	*Normal LV n=35*	*Abnormal LV n=91*	*p value*
Age (years)	53.0+/-9.9	50.0+/-9.8	p=0.070
Sex (%men)	65.6	65.9	p=0.502
Duration of RRT (months)	26.2+/-22.7	33.2+/-31.6	p=0.121
HD vs. PD (% on HD)	34	69	p=0.001*
Systolic BP (mmHg)	126.0+/-18.5	139.4+/-22.6	p=0.023*
Diastolic BP (mmHg)	74.9+/-9.6	82.2+/-11.6	p=0.002*
PMH of IHD (%)	23	15	p=0.249
PMH of Diabetes (%)	8.6	18.7	p=0.029*
PMH of CHF (%)	5.7	9.9	p=0.321
PMH other vascular (%)	0	8	p=0.071
Haemoglobin (g/do)	11.8+/-1.5	11.4+/-1.8	p=0.186
Cholesterol (mmol/L)	6.2+/-1.7	5.5+/-1.7	p=0.818
BNP (picomoles/L)	26.0	166.5	p=0.001*

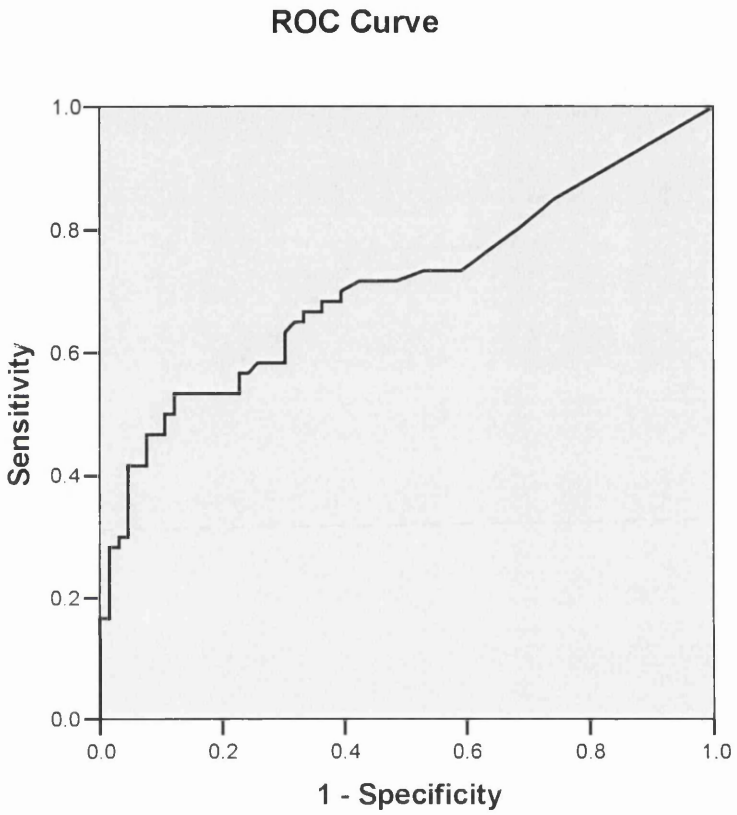
*significant result with $p<0.05$

Table 7.2 LV abnormalities measured using CMR imaging in BNP cohort

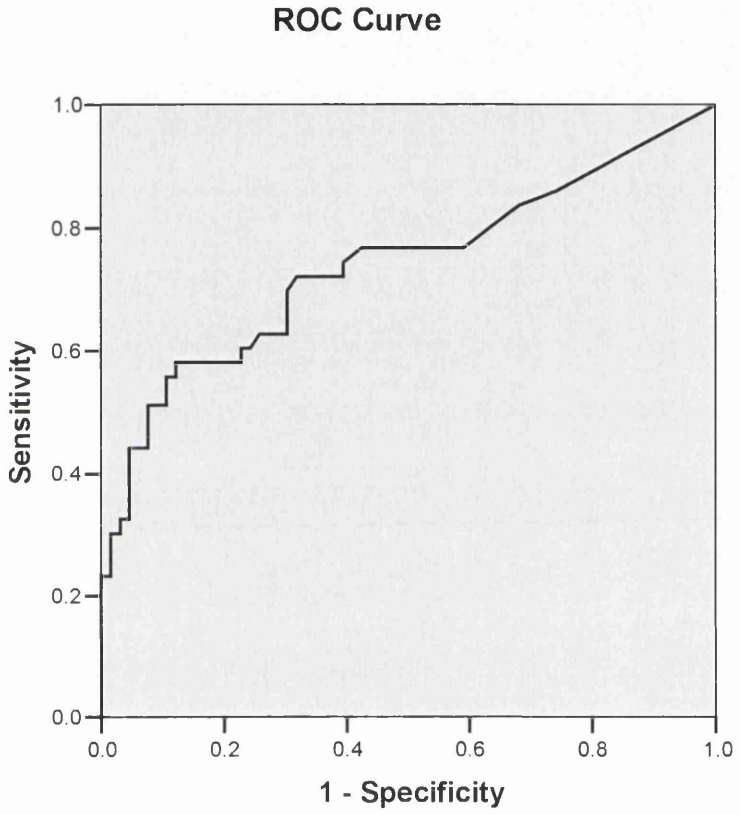
Variable	*Normal LV n=35*	*Abnormal LV n=91*	*p value*
Ejection Fraction (%)	68+/-7.6	65+/-14.1	p=0.147
LVMI (g/m^2)	74.3+/-12.3	116.1+/-32.9	P<0.0001*
ESVcorrected to BSA (ml/m^2)	17.1+/-5.6	31.3+/-25.9	P<0.0001*
EDVcorrected to BSA (ml/m^2)	57.7+/-18.7	84.9+/-30.4	P<0.0001*

*significant result with $p<0.05$

Graph 7.5 Receiver-operator characteristic curve demonstrating ability of BNP to detect an abnormal LV. Area under the curve = 0.707



Graph 7.6 Receiver-operator characteristic curve demonstrating ability of BNP to detect LVH. Area under the curve = 0.739.



Graph 7.7 Receiver-operator characteristic curve demonstrating ability of BNP to detect LVSD. Area under the curve = 0.845

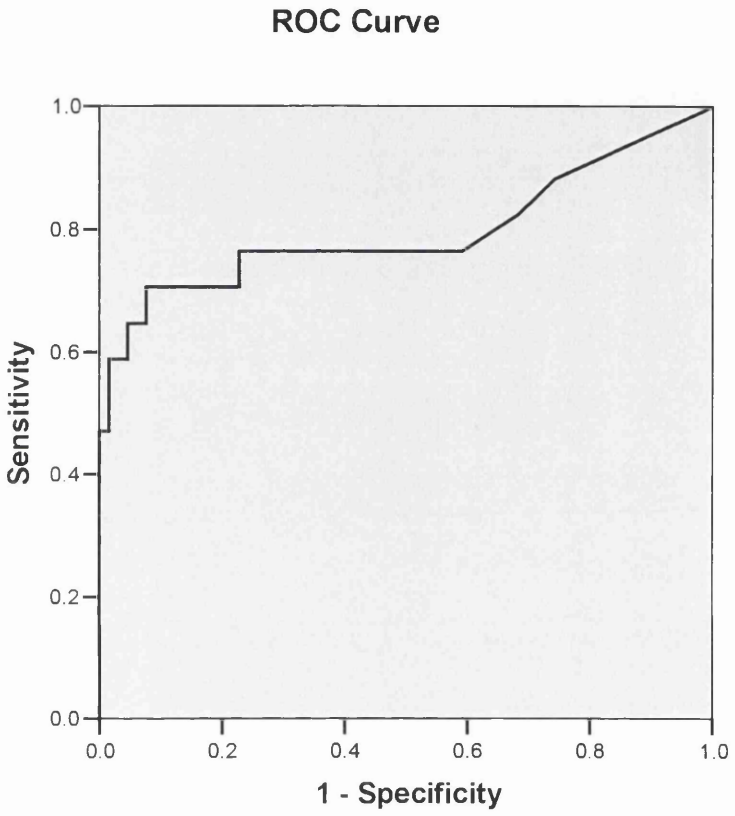


Table 7.3 The usefulness of BNP to detect LV abnormalities in patients with ESRF felt suitable for renal transplantation

	Any LV abnormality	*LVH*	*LVDil*	*LVSD+LVH+LVDil*
sensitivity	65%	63%	68%	77%
specificity	79%	79%	79%	79%
PPV	88%	79%	80%	67%
NPV	59%	60%	68%	90%
Accuracy	71%	74%	76%	80%

Table 7.4 Univariate and multivariate predictors of BNP in patients with ESRF felt suitable for renal transplantation. (Adj R square = 0.297 for multivariate regression model)

Variable	*Univariate testing*	*Regression Model*
Ejection Fraction	p=0.006	p=0.043, β=-0.171
EDV	p=0.005	NS
ESV	p=0.001	NS
LV mass index	p<0.001	p<0.001, β=0.435
Systolic BP	p=0.035	NS
Diabetes	p=0.043	NS

Chapter 8

The Relationship between Left Ventricular Abnormalities and Coronary Artery Disease

8.1 Introduction

When considering investigation for a patient with symptoms of heart failure and impaired LV systolic or diastolic function, CMR imaging with LGCE is now an established Class 1 indication for differentiating ICM from NICM. Furthermore, evidence is accumulating that this technique identifies patients who have been wrongly labelled as having NICM when the diagnosis is in fact ICM. In the study of McCrohon *et al.* (225), 13% of patients who had previously been diagnosed with NICM, on the basis of results from QCA, displayed patterns of regional wall thinning and LGCE typical of ICM. It is well recognised that recanalisation after an occlusive coronary event or embolization from a minimally stenotic but unstable plaque occurs, and post mortem studies have documented patterns of fibrosis indistinguishable from myocardial infarction in patients with a pre-mortem diagnosis of NICM. Obviously this misclassification has implications for both treatment and prognosis for the patient concerned and wider implications regarding the need for family screening.

The prevalence of CAD in patients with ESRF is high and angiographic studies of patients established on RRT have estimated that 50% have underlying CAD. However, patients are often asymptomatic or have non-specific symptoms such as breathlessness which could be attributed to CAD, underlying cardiomyopathy, anaemia or fluid overload. Furthermore, as the prevalence of CAD and LV abnormalities are high in

patients with CRF and they both occur early in the course of progressive renal failure, defining the relationship between CAD and uraemic cardiomyopathy has been difficult.

The high prevalence of LV abnormalities in patients with ESRF also affects interpretation of non-invasive stress testing, especially ETT and DSE, resulting in a lower sensitivity and specificity of these techniques in patients with ESRF compared to the normal population. Stress testing forms an important part of cardiac risk assessment when considering patients for renal transplant but the inconclusive results that are often obtained mean that a high proportion of patients undergo invasive diagnostic coronary angiography.

We hypothesised that a CMR study, using a combination of LGCE and standard CMR cine imaging would help us gain insight into the relationship of LV abnormalities to CAD and that such a CMR study may be a stronger predictor of significant underlying CAD than the currently used non-invasive techniques in this population. We therefore studied 60 patients undergoing assessment for renal transplantation, with no prior history of AMI, using a combination of assessment of LV function, mass and volumes, wall motion scoring and LGCE in addition to the usual methods of assessment of CAD to test this hypothesis.

8.2 Methods

8.2.1 Subjects

Patients were recruited from the West of Scotland renal transplant waiting list or directly from the renal transplant assessment clinic at the Western Infirmary, Glasgow. All patients gave informed consent and the study had approval from the local ethics committee.

8.2.2 Procedure

All patients attended for screening on a post-dialysis day. All medications were taken as usual. Sixty patients underwent the protocol as described in Chapter 2, along with the extended CMR protocol including LGCE. Patients with a prior history of AMI were excluded from this part of the study.

8.2.3 Statistics

Statistical analysis was performed using SPSS Version 11.5 software (SPSS inc. Chicago IL, USA). Baseline data are expressed as mean +/- SD or median, if not normally distributed. Differences between the groups were assessed using a two-sample t test (normally distributed data) or Mann Whitney U test (nonparametric data). A p-value of less than 0.05 was considered significant. 95% confidence intervals for differences between groups in mean percentage change from baseline are given. Correlations between continuous values were assessed using Pearson's correlation coefficient for parametric data.

8.3 Results

8.3.1 Baseline Characteristics

Data was available for 60 patients who underwent the extended CMR protocol involving LGCE. Baseline characteristics for this cohort of patients are shown in Table 8.1. Average age of the cohort was 52 years of age, ranging from 27-70 years of age. Three-quarters of the cohort were men and on average, patients had spent 30 months on dialysis and 15% had undergone previous renal transplantation. With regard to standard CV risk factors, no patient had a prior history of CHF or AMI and 15.5% had a previous history of IHD. Almost one fifth of the cohort were diabetic (19%) and 34.5% had a history of hyperlipidaemia. Less than half the cohort had never smoked (44.5%) and 34.5% were current smokers. As observed in previous chapters, the majority of the cohort had a history of hypertension (91.4%) and 22.4% had a family history of premature IHD.

Average BP for the cohort was high with an average systolic BP of 138+/-23.2mmHg and an average diastolic BP of 81+/-10.1mmHg. Average cholesterol was 5.8+/-1.4mmol/L and average haemoglobin concentration for the cohort was 11.5+/-1.5g/dL.

Differences in baseline characteristics between the whole of the initial cohort of 149 patients and the 60 patients who underwent LGCE are displayed in Table 8.1. Compared to the total initial cohort, the only significant difference found with regard to baseline characteristics in those who underwent the extended CMR protocol with LGCE, was a history of CHF. Patients who were given LGCE, reflecting the fact that patients with previous AMI were excluded from this part of the study, had a much lower prevalence of previously documented CHF and in fact, excluding those patients with a previously documented AMI also resulted in the exclusion of those with previously documented

LVSD in this cohort. There were no other significant differences with regard to renal history, other co-morbidity and standard CV risk factors between the groups.

8.3.2 Left ventricular abnormalities

The results of baseline CMR cine imaging are shown in Table 8.2 along with the normal reference ranges. Similar to the initial cohort, there was a high prevalence of LVH and 73.3% of the cohort (44 patients) had an elevated LVMI. Despite the fact that no patient had a history of LVSD before screening, 7 patients (11.7%) were found to have LVSD as defined by CMR imaging. These patients had associated LVDil and LVH and overall, 10 patients (16.7%) had a dilated LV and therefore 3 patients were defined as having eccentric LVH.

Average LVMI was much higher in both men and women compared to the normal ranges with similar ranges for volumes and function, compared to the sex matched normal reference range. Of note, the female group had relatively lower LV volumes than the normal reference range and a higher mean EF, a finding most likely associated with the high prevalence of LVH, whereas in the male group there was little difference from the normal range with regard to LV function or volumes.

8.3.3 Late gadolinium contrast enhancement

Initially the cohort was split into two groups on the basis of presence or absence of LGCE during the CMR scan. Of the 60 patients making up the cohort, 16 (26.6%) had evidence of LGCE. Differences between the groups with regard to baseline characteristics and baseline LV measurements are shown in Table 8.3 and Table 8.4 respectively. There was

no significant difference in age between the two groups (55+/-8.8 years vs. 52+/-9.3 years, p=0.214) and no significant differences with regard to past renal history, including length of renal failure (p=0.887), length of RRT (p=0.667), type of dialysis therapy (p=0.250) and history of a previous renal transplant (p=0.843). Patients who were found to have LGCE, indicating myocardial necrosis or fibrosis, were more likely to be male (94% vs. 67%, p=0.033), diabetic (40% vs. 11.6%, p=0.017) and have a history of IHD (33.0% vs. 9.3%, p=0.028). However, patients with LGCE did not have significantly higher systolic (p=0.298) or diastolic (p=0.650) BP compared to those without LGCE and similar proportions in both groups had a history of hypertension (93% vs. 91%, p=0.756) and were smokers (33% vs. 35%, p=0.667). Although a higher proportion of patients with LGCE had a history of hyperlipidaemia (47% vs. 30%, p=0.253), this did not reach statistical significance and was likely to reflect a higher level of awareness of hyperlipidaemia in this group due to a higher prevalence of IHD.

With regard to biomarkers, although both BNP (lgBNP 4.8 vs. 2.8, p=0.283) and CRP levels (27 vs. 7, p=0.089) were higher in the LGCE positive group, neither reached statistical significance. Patients with LGCE had a significantly lower total serum cholesterol than those without LGCE (5.1+/-1.0mmol/l vs. 6.1+/-1.5mmol/L, p=0.009), again reflecting a higher prevalence of IHD (33.0% vs. 9.3%) and statin prescription (40% vs. 29%) in the LGCE group, and there was no difference in mean haemoglobin values between the two groups (11.6+/-2.0g/dL vs. 11.5+/-1.3g/dL, p=0.732).

The differences between the patients found to have LGCE and those who did not, with regard to LV measurements, are displayed in Table 8.4 and Graphs 8.1-8.4(a). Patients who displayed LGCE had significantly higher LVEDV (87.6+/-26.5ml/m^2 vs. 72.2 +/-

20.8ml/m^2, p=0.043), LVESV (36.3+/-21.9ml/m^2 vs. 20.3+/-7.1ml/m^2, p=0.034) and LV mass (118.0+/-34.3g/m^2 vs. 99.4+/-24.3g/m^2, p=0.05) than those without LGCE and significantly lower EF (59+/-11.5% vs. 71+/-5.8%, p<0.001).

All 7 patients with LVSD were found to have LGCE on CMR scanning and these patients all had associated LVDil. Only 3 of the 10 patients with a dilated LV did not show LGCE on CMR scanning and these were the 3 patients who were found to have eccentric LVH. This was reflected in the finding that whereas a high proportion of patients in the LGCE group had LVSD (43%) and LVDil (43%), the only LV abnormality that was prevalent in the group without LGCE was that of LVH and similar proportions of patients in both the LGCE positive and negative groups had LVH (76% vs. 72%).

8.3.4 Patterns of late gadolinium contrast enhancement

Within the group of patients displaying LGCE, the distribution of LGCE showed 2 different patterns. Whereas the majority showed a subendocardial pattern, confined to a particular coronary artery territory and typical of that caused by AMI secondary to CAD, a smaller proportion showed a more 'patchy' distribution not confined to a particular coronary artery territory and throughout the myocardium without confinement to the subendocardial layer. This pattern of LGCE was more typical of that reported to be associated with hypertrophic cardiomyopathy. Of the 16 patients found to have LGCE, 5 patients (31%) displayed a patchy distribution of LGCE whereas the other 11 patients (69%) displayed the more discrete subendocardial pattern of LGCE.

Differences in LV measurements between those displaying the two different types of LGCE as well as those with no LGCE are displayed in Table 8.5 and Graphs 8.1-8.4(b).

Patients displaying the discrete pattern of LGCE, consistent with ICM, had the lowest mean EF (56+/-12.4%) compared to those with patchy LGCE (66+/-5.7%) or no LGCE (71+/-5.8%) and patients displaying the patchy pattern of LGCE, consistent with NICM had a relatively higher LV mass (126.2+/-34.6g/m^2) than either those with discrete LGCE (114.6+/-35.3g/m^2) or those with no LGCE (99.4+/-24.3g/m^2). This finding was reflected in the fact that all 5 patients displaying patchy LGCE had LVH and all 7 patients with LVSD had focal LGCE. The only significant difference between those patients with discrete LGCE and those with patchy LGCE, was EF (p=0.05). Although LV mass was higher in those patients with patchy LGCE compared to those with discrete LGCE this did not reach statistical significance (p=0.547). This was most likely due to the small number of total patients displaying a patchy distribution of LGCE.

With regard to baseline characteristics and standard CV risk factors, no differences were found between those with a patchy distribution of LGCE and those without LGCE for any variable with regard to past renal history, standard CV risk factors including systolic and diastolic BP, age and sex or biomarkers such as BNP and CRP. Again, this was likely influenced by the small number of total patients displaying a patchy pattern of LGCE on CMR scanning. Patients with a discrete pattern of LGCE, were older (58+/-7.7 years vs. 52+/-9.3 years, p=0.034), more likely to be male (100% vs. 67%, p=0.023), diabetic (45.5% vs. 11.6%, p=0.011) and more likely to have a past medical history of IHD (45.5% vs. 9.3%, p=0.004). Patients with discrete LGCE had lower total cholesterol levels compared to those with no LGCE (4.7+/-0.8mmol/L vs. 6.1+/-1.5mmol/L, p=0.001), again reflecting a higher prevalence of IHD and resultant statin prescription (45.5% vs. 29%).

Finally, there were no significant differences between those with discrete LGCE and those with no LGCE with regard to either BNP (lgBNP 3.8 vs. 2.8, p=0.745) or CRP (34 vs. 7, p=0.128) levels.

8.3.5 Late gadolinium contrast enhancement and natural history of left ventricular abnormalities

Of the initial 60 patients who underwent the extended CMR protocol, 54 patients returned for a follow up CMR scan at least 6 months after the initial scan. Of these 54 patients, 14 displayed LGCE. Overall, there was no significant difference between baseline scan and that of follow up with regard LV mass, EF or volumes and there were no significant differences with regard to LV anatomy or function with follow-up in the group who did not display LGCE on CMR scanning. Turning to those patients who did have LGCE on CMR scanning, again, overall there was no significant progression or regression of LV mass, function or volumes with follow-up. Of the 14 patients who displayed LGCE on CMR scanning, 11 of these displayed a focal pattern of LGCE and changes in LV parameters with follow-up are displayed in Table 8.6. With follow-up, although the trend was towards a fall in EF, with corresponding increase in LV mass and volumes, none of these parameters reached statistical significance.

8.3.6 Coronary angiography and left ventricular abnormalities

Within the total cohort of 148 patients, 38 patients underwent coronary angiography. One patient developed a significant right femoral pseudoaneurysm requiring vascular surgery. There were no other major adverse events recorded as a result of angiography. Of the

patients undergoing angiography, 15 (41%) were found to have either normal coronary arteries or mild disease only. This was despite the fact that referral for angiography was only made if patients had a positive stress test, LVSD or at specific request of the referring physician.

The differences found for LV parameters and BP between the group of patients who were found to have severe CAD at QCA, defined as a coronary artery stenosis of >70%, and those who were found to have mild CAD or normal coronary arteries are shown in Table 8.7. EF was significantly lower in the group of patients with severe CAD (53+/-17% vs. 67+/-11%, p=0.013) and ESV was significantly higher (51+/-37ml/m^2 vs. 28+/-25ml/m^2, p=0.049). Although both EDV (99+/-37ml/m^2 +/- 77+/-40ml/m^2, p=0.116) and LVMI (123+/-34g/m^2 vs. 112+/-47g/m^2, p=0.447) were higher in patients with CAD, neither of these reached statistical significance. Interestingly, both systolic BP and diastolic BP were lower in patients with severe CAD although the differences observed failed to reflect statistical significance. Lower mean BP in patients with severe CAD may reflect either a lower EF, or a higher prescription of cardioprotective medication in the group found to have severe CAD, or a combination of both.

There were other differences observed between patients with severe CAD and those with milder disease or normal coronary arteries. Patients with severe CAD were older 54+/-9 years vs. 48+/-8 years, p=0.041), more likely to be male (90% vs. 64%, p=0.032) and more likely have a history of IHD (62% vs. 21%, p=0.044). There was no difference between the groups with regard to length or type of RRT or with regard to haemoglobin level. Also, there was no significant difference found between the groups with regard to prevalence of diabetes (38% vs. 43%, p=0.459). This may be due to the selection bias of

diabetic patients undergoing coronary angiography (70% of patients undergoing angiography had a history of diabetes)

8.3.7 Coronary angiography and late gadolinium contrast enhancement

Within this cohort of 60 patients who underwent CMR with LGCE, 15 patients had coronary angiography (25% of cohort). Within this group, 9 patients were found to have severe CAD and of these patients, 8 displayed a discrete pattern of LGCE consistent with ICM. One patient with significant CAD did not display any pattern of LGCE and one patient did display discrete LGCE and was found to have plaque disease at angiography. Two patients displaying a patchy pattern of LGCE underwent coronary angiography and were found to have non-obstructive plaque disease. The presence of LGCE significantly correlated with severe CAD ($p=0.008$, $r=0.659$).

The sensitivity of LGCE pattern on CMR scanning to detect severe CAD was 91% and the specificity 75%. The corresponding NPV and PPV were 75% and 91% respectively and overall accuracy of the technique was 87% (Table 8.8).

8.3.8 Exercise tolerance testing

Patients also underwent the usual methods of non-invasive assessment for underlying CAD prior to renal transplantation in the West of Scotland (Flowchart 2.1). Of the initial cohort of 148 patients who were already awaiting renal transplant or undergoing assessment for transplant, 119 (82.1%) attempted ETT and 26 patients felt unable to attempt even Stage 1 of a Full Bruce protocol. Of the patients who did undergo ETT, the average time exercised was 6 minutes and 50 seconds with a range of 1-14 minutes. The

range of exercise times for men and women are displayed in Graph 8.5. Of the 119 patients who underwent ETT, 33 patients did not manage to exercise for the minimum time period of 6 minutes (7 METS) and therefore had an inconclusive ETT. Thus in total, 42.5% of the cohort either refused ETT or performed inadequately during exercise for the ETT to be of diagnostic use.

Of those patients who did undergo ETT, 24 also had a coronary angiogram and 16 of these 24 patients were identified to have severe CAD. No correlation was found between whether or not ETT was attempted or total exercise time attained. However, there was a significant correlation between the finding of severe CAD at angiography and the presence of ST changes during exercise ($p=0.001$, $r=0.644$). The sensitivity of ETT to detect severe underlying CAD was found to be 42% and the specificity 80%. The corresponding NPV and PPV were 30% and 88% respectively reflecting a relatively high number of false negative tests and the overall accuracy of the technique was 50% (Table 8.8).

8.3.9 Radionuclide stress perfusion imaging

Of the total initial cohort, 39 patients underwent radionuclide stress perfusion imaging, usually as a result of failure to perform adequately at ETT. Of these patients, 14 went on to have a coronary angiogram. Of the patients who underwent angiography, 7 were found to have severe CAD. Of the 14 stress perfusion studies carried out only 3 were reported as normal. No correlation was found between the finding of a reversible perfusion defect and significant CAD. However, there was a significant correlation between the finding of a fixed perfusion defect and CAD ($p=0.08$, $r=0.600$). The sensitivity of radionuclide

imaging to detect significant CAD was 87% with a specificity of only 33%, reflecting a relatively high number of false positive stress perfusion tests. The NPV and PPV were 67% and 64% respectively and the overall accuracy of the technique to detect severe CAD was 64% (Table 8.8).

8.4 Discussion

The technique of CMR imaging with LGCE is now an established sensitive and specific method for the non-invasive differentiation of ICM from NICM. Patel *et al.* (226) recently investigated 234 consecutive patients presenting with LVSD, with an EF of less than 30% and an unclear aetiology for the cardiomyopathy. Patients underwent both CMR with LGCE and coronary angiography, and the authors concluded that a diagnosis of ICM could be correctly established by LGCE with a sensitivity of 92% and a specificity of 93%, compared to the reference standard of QCA. Furthermore, in the study of McCrohon *et al.* (225), all patients with ICM, defined by QCA, displayed the typical pattern of LGCE associated with AMI. An important finding of our study is the fact that all patients in this cohort with LVSD and the majority with LVDil had an underlying ICM, with evidence of previous AMI. The fact that LVSD was not found without evidence of AMI in this study suggests that the aetiology of LVSD in this cohort is CAD rather than a dilated form of hypertrophic cardiomyopathy or eccentric cardiomyopathy secondary to volume overload. The findings from the previous longitudinal echocardiographic study of Parfrey *et al.* (29), in patients with ESRF and no history of IHD, provides supportive evidence of the proposal that LV systolic function is dependant on CAD in this population. They identified, in a cohort of 432 patients with ESRF, that LVSD was the strongest predictor of the development of de novo IHD during follow-up and underlying IHD was also identified as a risk factor for LVDil and LVSD in further work by Parfrey *et al.* (71). It could therefore be proposed that silent CAD and AMI preceded the development of LVSD and symptoms of IHD in the former study and that

LV remodelling post AMI was responsible for the association between IHD and LVDil in the latter study.

Using the technique of LGCE in this cohort of 60 patients with no previous history of AMI, we found that 11 (18.3%) patients had evidence of previous AMI, including 6 (10%) patients who had no prior history of IHD. It is important to identify these patients in an attempt to improve the poor prognosis of patients with ESRF after AMI by targeting risk factors such as hyperlipidaemia, hypertension and smoking habits as well as establishing secondary preventative therapy such as aspirin, beta-blockers and ACEI's which have been shown to improve outcome in this population post AMI (166,170). These patients were asymptomatic at the time of screening, and in the case of those with preserved LV systolic function, unless they developed symptoms of limiting angina there is no evidence that proceeding to coronary angiography and revascularisation will improve outcome (177). It is also unclear whether revascularisation of IHD in the presence of an associated ICM improves outcome in this population, although in the normal population if a patient has significant CAD and hibernating myocardium is documented, revascularisation by way of PCI or CABG will be undertaken, although trials such as the STICH trial (273) are ongoing to investigate whether revascularisation is beneficial versus medical therapy in such patients.

Patients displaying the pattern of LGCE typical of CAD and previous AMI were more likely to be older, male, diabetic and have a previous history of IHD. These are typically the risk factors previously identified in this population for CAD by several authors (29,274). Although these patients were more likely to be on secondary prevention than those without focal LGCE, 45% were not prescribed aspirin, 54% were not prescribed a

statin, 33% were not prescribed a beta-blocker and 42% were not prescribed an ACEI or ARB at the time of screening. Overall systolic BP of patients with focal LGCE was 142+/-28.3mmHg and mean diastolic BP was 80+/-8mmHg. The use of LGCE has therefore identified patients with previously unrecognised AMI and therefore those with a poorer prognosis on the transplant waiting list and those in whom potential reversible risk factors should be more aggressively treated.

A smaller number of patients displayed a different pattern of LGCE, that of 'patchy' enhancement which was not confined to the subendocardium or to any particular epicardial coronary artery territory. This pattern of LGCE was only found in patients with LVH and showed similarities to the pattern described in previous studies using LGCE in patients with HCM (230,233,235). In the case of HCM, LGCE has been shown to be representative of areas of focally increased collagen replacement of myocardial cells, rather than myocardial disarray and is proportional to the total LV mass (235). It has also been shown that the presence of LGCE may independently predict prognosis in patients with HCM, and the presence of LGCE in patients with HCM is associated with the clinical markers of sudden death and progression to heart failure (233).

Pathological studies in patients on haemodialysis by means of endomyocardial biopsy have shown severe interstitial fibrosis, myocyte hypertrophy and disarray. In a study by Aoki *et al.* (258), 40 patients with LVDil and LVSD but normal coronary arteries underwent endomyocardial biopsy. The results showed histological changes typical of the dilated phase of HCM. They found the extent of myocardial fibrosis in biopsy specimens to be predictive of cardiac death. In studies of patients with HCM and normal renal function, LGCE is more likely to be observed in patients in the dilated phase of

cardiomyopathy compared to the undilated, earlier phase (233,275). Thus, although it is likely that ICM is responsible for the majority of LVSD associated with uraemic cardiomyopathy, the dilated phase of concentric hypertrophic cardiomyopathy associated with uraemia is responsible for a smaller proportion. In the study of Aoki et al. (258) the 40 patients studied with dilated cardiomyopathy and normal coronaries made up 13% of the total cohort of 286 studied and CAD was found in 65%. We did not observe any patients with LVSD and either patchy LGCE or no LGCE. This may be partly explained by the fact that our cohort only included those patients felt to be suitable for renal transplantation whereas the study of Aoki *et al.* included patients from the general haemodialysis pool.

The number of patients in our study was small and only 7 patients were found to have LVSD at baseline scanning. However, we have since published results on a larger series of 134 patients with ESRF using LGCE and found similar results in a total of 11 patients with ESRF and LVSD undergoing assessment for renal transplantation (276). All 11 patients had evidence of previous AMI. Again, the number of patients in this study with a patchy distribution of LGCE is small but in the larger subsequent cohort this pattern of LGCE was observed in a total of 19 patients with a similar association of elevated LV mass but preserved LV function.

The results of this study therefore support the findings of Chapter 4. Rather than concentric and eccentric cardiomyopathy comprising the two predominant forms of cardiomyopathy in patients with ESRF with both culminating in LVSD, concentric hypertrophic cardiomyopathy and ICM are the two predominant forms with a much smaller contribution from primary eccentric/dilated cardiomyopathy. The presence of LV

dilation or LVSD should precipitate investigation for CAD but of course the goal should be early identification of those with underlying CAD before ischaemia and AMI result in LVSD and subsequent adverse remodelling.

It is well recognised that post AMI, the ventricle undergoes remodelling with associated increase in LV volume and mass (277). In this cohort there was a trend towards an increase in both LV volumes and mass with follow-up in patients with evidence of previous AMI, suggesting ongoing LV remodelling. The patients displaying a pattern of discrete LGCE also had significantly higher LV mass than those without LGCE at baseline scanning and it is likely that this is due to a combination of initial concentric hypertrophy associated with hypertension in progressive renal failure, and remodelling post AMI. Patients with LGCE were also more likely to be male and diabetic and both these factors are associated with higher LV mass compared to women and non-diabetics (64) and this should also be taken into consideration.

As in previous studies involving patients with ESRF (33,172-174), the usefulness of ETT and radionuclide imaging to identify patients with severe CAD was disappointing. A high number of false negative ETT studies meant that the overall accuracy of ETT to detect severe CAD was only 50% and a high number of false positive radionuclide studies severely affected the specificity of this test and led to an overall accuracy of just 64%. It may be that a combination of both tests in all patients may lead to an improved overall accuracy but due to the protocol followed in this study we were unable to test this hypothesis.

The identification of LGCE, a test not involving stress, in this study was a more accurate method of identifying patients with severe CAD. The overall accuracy of this test was

87% and the NPV was also better than that of either ETT or radionuclide imaging. However, the NPV was still relatively low at 75% suggesting that the addition of a stress imaging modality complimenting this technique would be preferable to a resting technique alone and may improve the NPV. However, the numbers of patients undergoing QCA in each group were small and very few patients underwent all three techniques in addition to QCA and these results should be interpreted with caution.

To better define the true relationship between LV abnormalities and CAD and to support these initial findings, patients with renal failure, normal ventricles and no symptoms of IHD would require repeated follow-up with CMR and LGCE to observe the developing pattern of abnormalities and this technique was felt to be capable of answering many of the remaining questions in this population without resorting to coronary angiography and/or myocardial biopsy. However, in light of recent evidence of an association between the administration of gadolinium based contrast agents and a condition known as nephrogenic fibrosing dermopathy (NFD) in patients with moderate to severe renal failure, as of June 2006 gadolinium based contrast agents have been used with caution in this population.

NFD was first described in 1997 (278), but it was not until 2006 that the association with gadolinium was made (279-280). NFD consists of a thickening of the skin, initially affecting the hands, feet and limbs but can progress to involve the trunks and buttocks. The thickened skin becomes indurated and can result in significant debilitation with contractures of the joints. The lesions themselves resemble those of scleroderma but there is no associated monoclonal gammopathy. Biopsy of the lesions shows dermal fibroplasia and electron microscopy of the samples has demonstrated gadolinium, detected in areas

of calcium phosphate deposition in blood vessels (281). Systemic involvement of the lungs, striated muscles and diaphragm has also been reported leading to an alternative name of nephrogenic systemic fibrosis (NSF) (282).

Patients developing the condition had been administered a gadolinium based contrast agent up to 18 months prior to the development of symptoms (283), almost invariably have ESRF (279-281) and are more likely to be on PD. NFD has very rarely been observed in patients who are not dialysis dependant. World wide around 220 cases have now been reported (283) and there is a registry on the U.S Food and Drug administration (FDA) MedWatch system for the reporting of new or suspected cases. The majority of patients who have developed NSF have done so after high doses of gadolinium contrast agent were administered for magnetic resonance angiography (MRA). Whether or not this condition is related to the dose of gadolinium based agent administered or whether it is an iatrogenic effect, remains to be established and it is unknown why some patients with ESRF have developed this condition while the majority have not, although concomitant acidosis and/or hypercalcaemia at the time of administration have been postulated (281) and a relationship to concomitant high dose erythropoietin has been suggested (284). It has also been found that a high proportion of patients who develop NSF, do so around 2 weeks after vascular surgery or an episode of deep venous thrombosis. In view of this observed association between NSF and gadolinium based contrast agent administration, the FDA published a health advisory in June 2006, updated in May 2007, regarding the use of these agents in patients with a GFR of <30ml/min (283) and as of May 2007 it is advised that patients with a GFR of <30ml/min do not receive gadolinium based contrast agents unless the information gained is deemed

potentially life saving. Similar guidelines have now been implemented by the UK based Medicine and Healthcare products Regulatory Agency (MHRA) but whereas all gadolinium based contrast agents are included in the warning from the FDA, only Omniscan and Magnevist are included in the statement from the MHRA and it is unclear whether other chelates with a cyclical structure, in which the gadolinium is more tightly bound, are associated with the same potential risks (285). It is therefore unlikely that further studies using gadolinium based contrast agents in patients with renal failure will be possible, although the ongoing development of intravascular CMR contrast agents, and improvement of other CMR sequences such as T2 weighted infarct imaging, the establishment of dobutamine stress CMR (DSCMR) imaging or BOLD perfusion imaging may provide alternative methods of tissue characterisation and stress imaging using CMR in this population. It should be mentioned that after 4 years of follow-up no patient in this cohort has developed signs or symptoms of NSF.

The results of this study suggest that CAD plays a more important role in the aetiology of uraemic cardiomyopathy than previously realised, especially the findings of LVDil and LVSD. It is clear that more accurate, non-invasive methods of detection of underlying CAD in patients with ESRF are required to identify those patients who may benefit from intensive risk factor modification and secondary prevention before the development of LVDil and LVSD. Rather than using a single method of stress imaging in this population, it may be that a combination of stress imaging tests such as radionuclide imaging in addition to DSE or DSCMR would provide complimentary information, improving overall accuracy and further research is required in this area. The recent improvements in

multidetector computed tomographic coronary angiography may also provide a future useful non-invasive means of anatomical assessment of CAD in this population.

Although this initial study has provided useful and unique information on the relationship between CAD and LV abnormalities, further studies using gadolinium based contrast agents are not currently possible. However, DSCMR has now been established clinically as a more sensitive and specific test than DSE for the diagnosis of CAD (286) and this technique provides accurate information regarding prognosis in both patients with suspected underlying CAD (287) and asymptomatic patients undergoing non-cardiac surgery (288). DSCMR does not require the administration of gadolinium based contrast agents and may provide a future useful means of non-invasive testing for CAD in this population.

Older patients with ESRF and resting LVDil or LVSD should undergo further, preferably non-invasive, investigation for underlying CAD. There is also an urgent need for prospective studies to establish whether revascularisation is beneficial in this population versus medical treatment in the current era. Patients with renal failure were not excluded from the recently published COURAGE trial (177) and sub group analysis involving patients with renal failure may provide much needed new evidence regarding PCI in the management of CAD in this population.

Table 8.1 Difference in baseline demographics between patients in LGCE cohort and total cohort

BASELINE VARIABLE	***LGCE cohort n=60***	***Total cohort n=148***
Age (years)	52+/-9.2	50 +/-10
Sex (%male)	75	68.2
Patients on haemodialysis (%)	64	60
Time on dialysis (months)	30+/-29	31.6 (0-144)
Length of renal failure (yrs)	12+/-10	8.2 (0.2-39)
Previous renal transplant (%)	15	18.6
History of IHD (%)	15.5	19.3
Family history of IHD (%)	22.4	26.4
History of chronic heart failure (%)	0*	7.6
Diabetic (%)	19	18.8
History of hypertension (%)	91.4	94.5
History of hyperlipidaemia (%)	34.5	36
Current smoker (%)	34.5	29.2
Systolic BP (mmHg)	138+/-23.2	136+/-24
Diastolic BP (mmHg)	81+/-10.1	80+/-12
Cholesterol level (mmol/L)	5.8+/-1.4	5.6+/-1.7
Haemoglobin (g/dL)	11.5+/-1.5	11.6+/-1.6

- *denotes significance $p<0.005$

Table 8.2 Baseline LV parameters for patients with ESRF undergoing CMR and LGCE with corresponding normal reference ranges.

MEN	**LGCE cohort**	**Normal range**
PARAMETER		
LVEDV	79(+/-25)ml/m²	82+/-15(53-112)ml/m²
LVESV	26(+/- 15)ml/m²	29+/-7(15-43)ml/m²
LVSV	50(+/-16)ml/m²	52+/-10(32-72)ml/m²
LVEF	66(+/-10)%	64+/-5(54-74)%
LVMI	110(+/-29)g/m²	65+/-9(47-83)g/m²
WOMEN		
LVEDV	69(+/-16)ml/m²	77+/-10(57-97)ml/m²
LVESV	19(+/-7)ml/m²	24+/-5(14-34)ml/m²
LVSV	50(+/-11)ml/m²	42+/-6(30-54)ml/m²
LVEF	72(+/-5)%	64+/-5(54-74)%
LVMI	89(+/-23)g/m²	52+/-8(36-68)g/m²

Table 8.3 Differences in baseline characteristics between patients with and without evidence of LGCE (*denotes significance at p<0.05)

BASELINE VARIABLE	***LGCE positive n=16***	***LGCE negative n=44***	***p-value***
Age (years)	55+/-8.8	52+/-9.3	p=0.214
Sex (%male)	94	67	p=0.033*
Patients on haemodialysis (%)	50	68	p=0.250
Time on dialysis (months)	33.5+/-33.8	29.2+/-28.5	p=0.667
Length of renal failure (yrs)	12.5+/-9.5	12.0+/-10.9	p=0.887
Previous renal transplant (%)	13.4	16.3	p=0.843
History of IHD (%)	33	9.3	p=0.028*
Diabetic (%)	40	11.6	p=0.017*
History of hypertension (%)	93	91	p=0.756
Hyperlipidaemia (%)	47	30	p=0.253
Current smoker (%)	33	35	p=0.667
Systolic BP (mmHg)	144+/-27.0	136.5+/-21.8	p=0.298
Diastolic BP (mmHg)	82+/-8.0	80+/-10.8	p=0.650
Cholesterol level (mmol/L)	5.1+/-1.0	6.1+/-1.5	p=0.009*
Haemoglobin (g/dL)	11.6+/-2.0	11.5+/-1.3	p=0.732
CRP	27+/-37	7+/-6	p=0.089
lg BNP	4.8	2.8	p=0.283

Table 8.4 Differences in baseline LV parameters between patients with and without evidence of LGCE

LV measurement	***LGCE positive n=16***	***LGCE negative n=44***	***p-value***
LVEF (%)	59+/-11.5	71+/-5.8	p<0.001**
LVEDV (ml/m²)	87.6+/-26.5	72.2+/-20.8	p=0.043*
LVESV (ml/m²)	36.6+/-21.9	20.3+/-7.1	p=0.034*
LVMI (g/m²)	118.0+/-34.3	99.4+/-24.3	p=0.05*
LVSV (ml/m²)	50.4+/-13.7	50.1+/-16.2	p=0.942
LVH (%)	76	72	p=0.732
LVDil (%)	43	4.7	p=0.001**
LVSD (%)	43	0	p<0.001**

- *denotes significance at p<0.05
- **denotes significance at p<0.005

Table 8.5 Differences in LV parameters between patients displaying patchy LGCE, discrete LGCE and those with no evidence of LGCE.

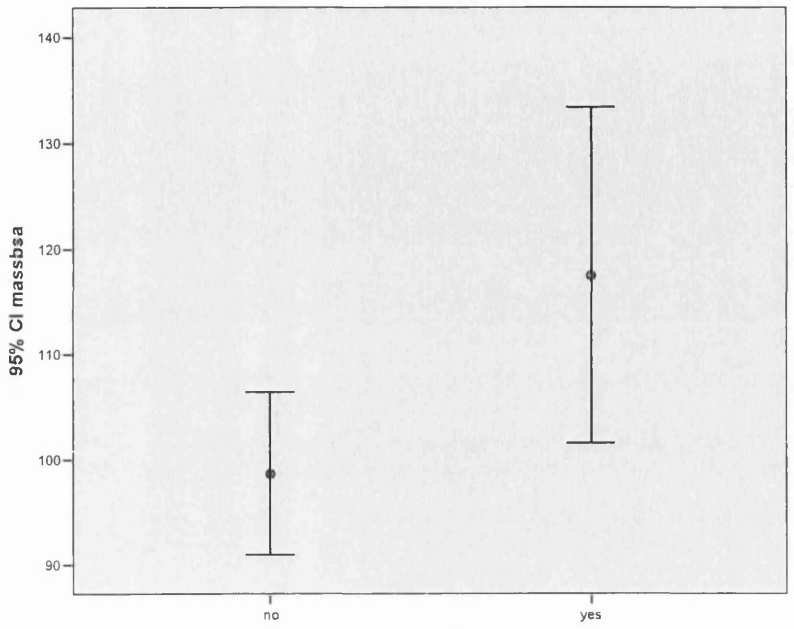
LV measurement	*LGCE negative n=44*	*Discrete LGCE n=11*	*Patchy LGCE n=5*
LVEF (%)	71+/-5.8	56+/-12.4*	66+/-5.7#
LVEDV (ml/m²)	72.2+/-20.8	87.2+/-27.0*	88.3+/-28.3
LVESV (ml/m²)	20.3+/-7.1	42.3+/-27.6*	29.8+/-11.7*
LVMI (g/m²)	99.4+/-24.3	114.6+/-35.3	126.2+/-34.6*
LVSV (ml/m²)	50.1+/-16.2	46.7+/-9.5	58.5+/-18.9
LVH (%)	72	67	100
LVDil (%)	4.7	42*	40
LVSD (%)	0	42*	0

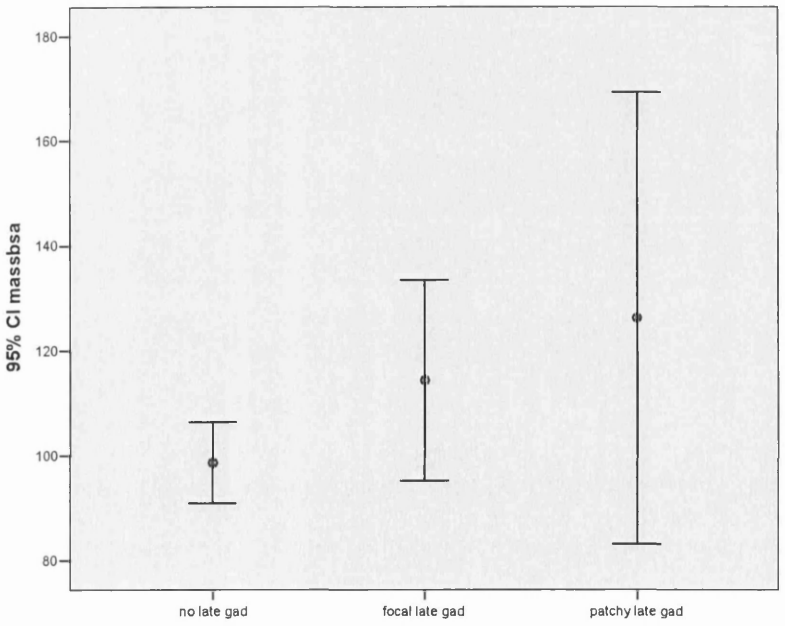
- * denotes significant difference compared to LGCE negative group ($p<0.05$)
- # denotes significant difference compared to discrete LGCE group ($p<0.05$)

Table 8.6 LV parameters at baseline and follow up in patients displaying discrete LGCE (n=11)

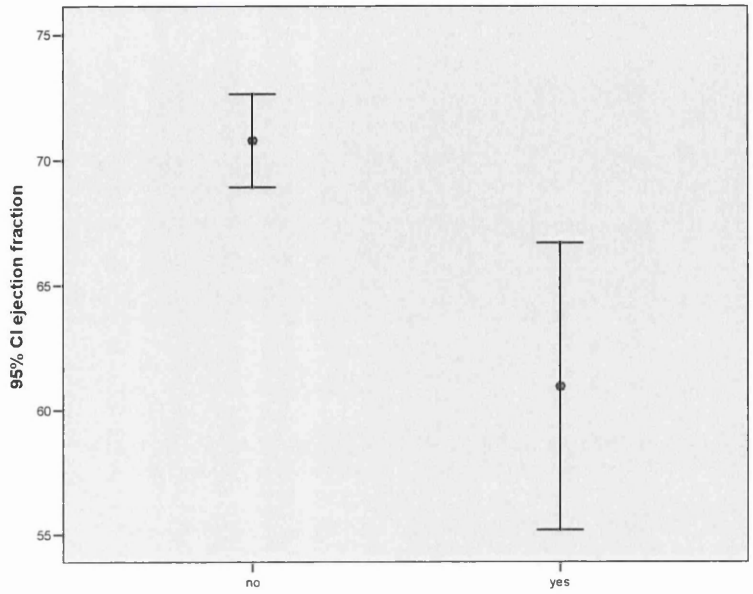
	Discrete LGCE (baseline)	**Discrete LGCE (follow-up)**	
PARAMETER			
LVEDV	79.3+/-21.5ml/m²	81.4+/-15.5ml/m²	p=0.719
LVESV	32.9+/- 17.0ml/m²	35.3+/-12.4ml/m²	p=0.577
LVEF	59+/-10.5%	57+/-14.0%	p=0.620
LVMI	104+/-25.0g/m²	110+/-18.6g/m²	p=0.248

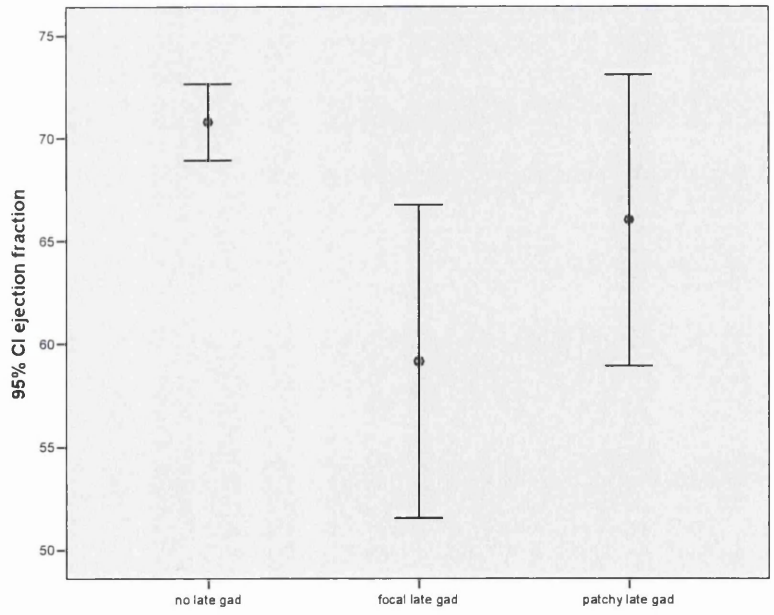
Graph 8.1 Difference in LVMI between patients displaying (a) no LGCE and LGCE; (b) no LGCE, discrete (focal) LGCE and patchy LGCE



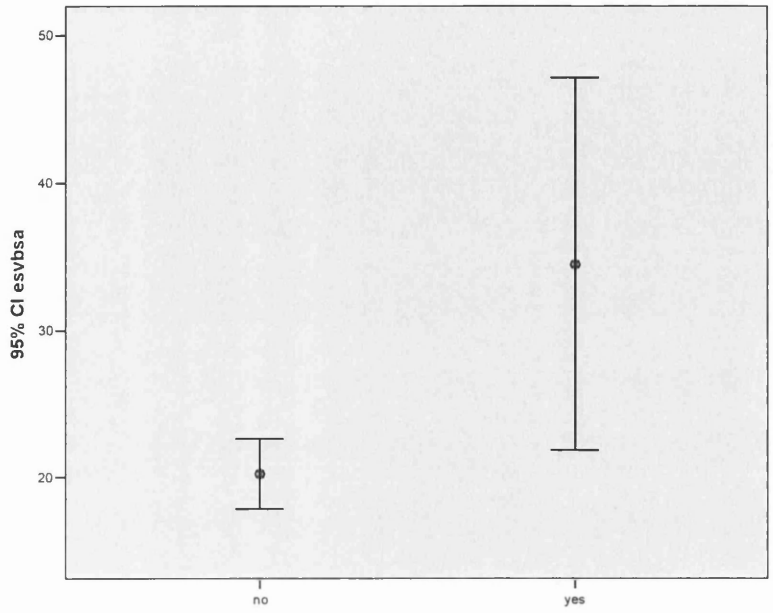


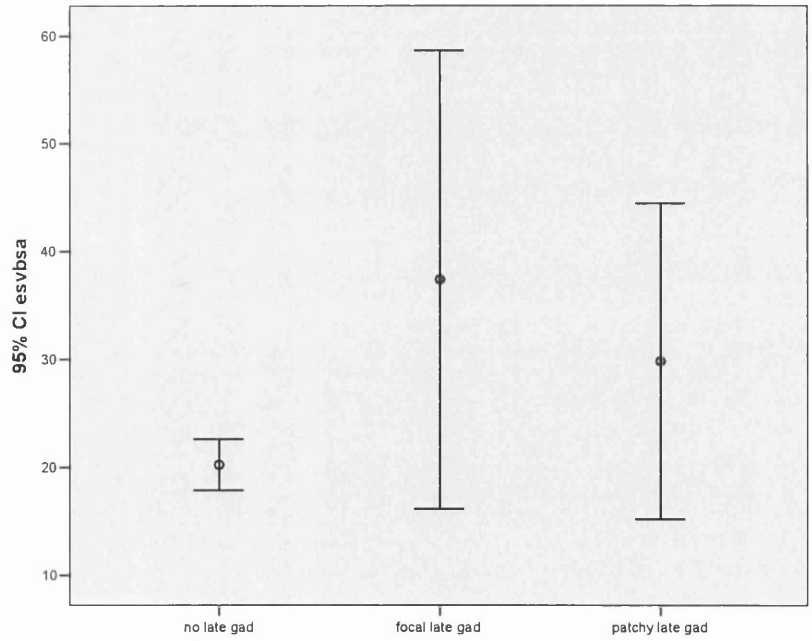
Graph 8.2 Difference in LVEF between patients displaying (a) no LGCE and LGCE; (b) no LGCE, discrete (focal) LGCE and patchy LGCE



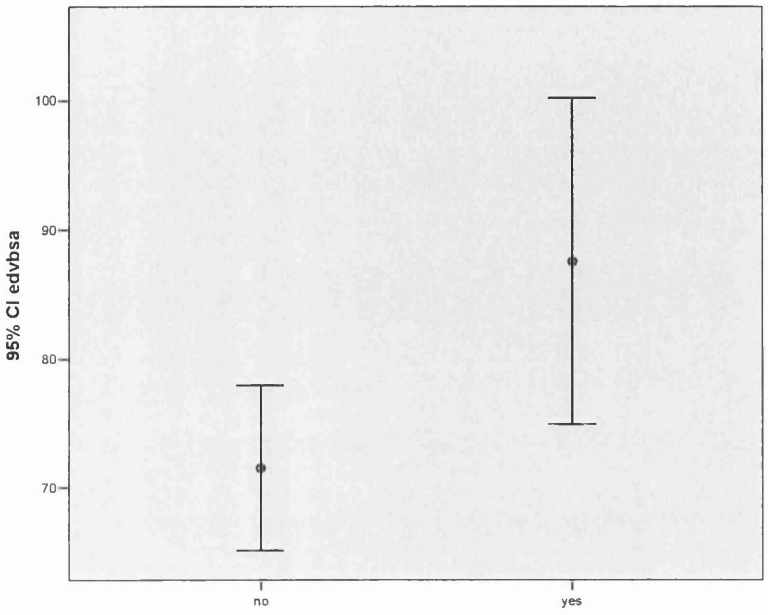


Graph 8.3 Differences in ESV between patients (a) displaying no LGCE and LGCE; (b) no LGCE, discrete (focal) LGCE and patchy LGCE





Graph 8.4 Differences in EDV between patients displaying (a) no LGCE and LGCE; (b) no LGCE, discrete (focal) LGCE and patchy LGCE



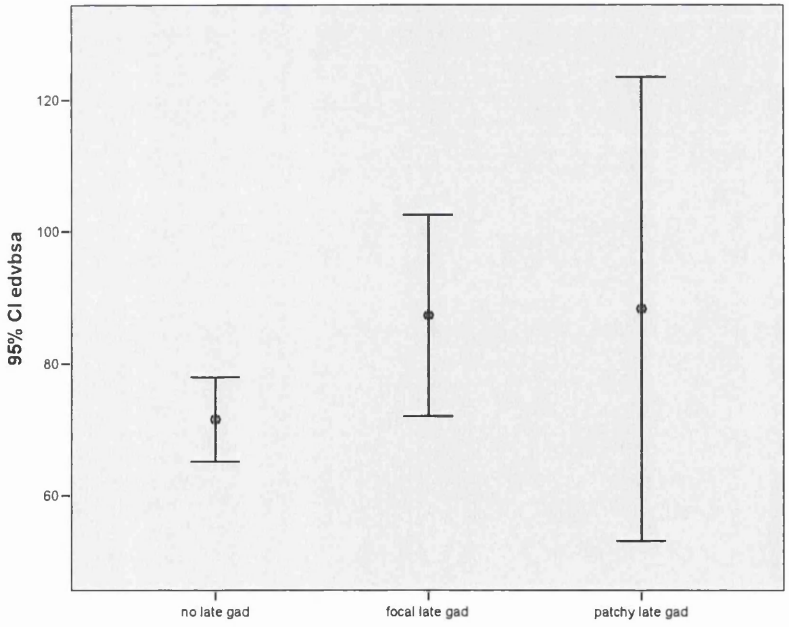


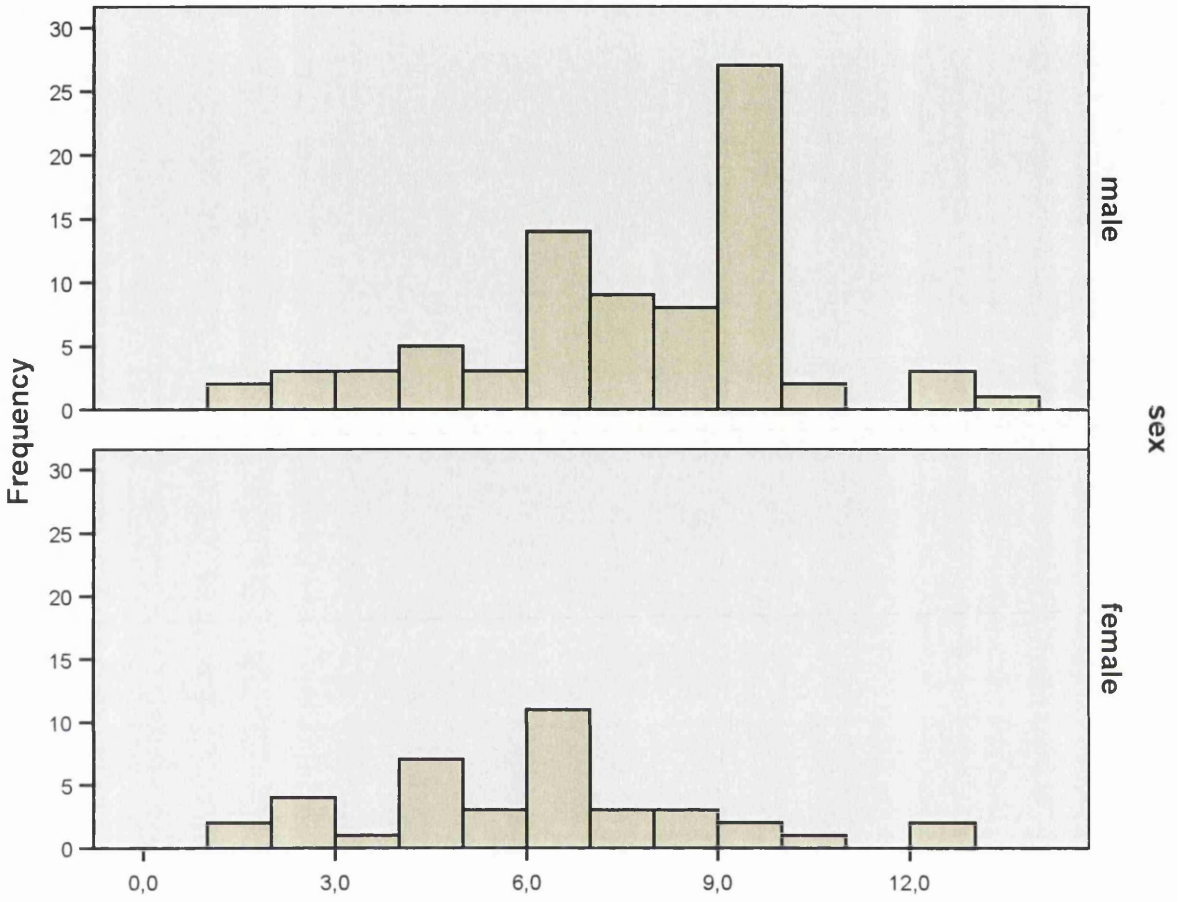
Table 8.7 Differences between LV parameters and BP for patients with and without severe CAD at QCA (* denotes significance, $p<0.05$)

Variable	*Severe CAD (stenosis>70%) n=23*	*Non-severe CAD (no stenosis>70%) n=15*	*p-value*
LVEF (%)	53+/-17	67+/-11	p=0.013*
LVMI (g/m^2)	123+/-34	112+/-47	p=0.447
EDV (ml/m^2) Corrected to BSA	99+/-37	77+/-40	p=0.116
ESV (ml/m^2) Corrected to BSA	51+/-37	28+/-25	p=0.049*
Systolic BP (mmHg)	133+/-26	147+/-26	p=0.143
Diastolic BP (mmHg)	76+/-11	83+/-13	p=0.092

Table 8.8 Usefulness of ETT, nuclear stress perfusion (SPECT) and LGCE with CMR to detect severe CAD

	ETT	*Nuclear perfusion*	*LGCE*
Sensitivity	42%	87%	91%
Specificity	80%	33%	75%
PPV	88%	64%	91%
NPV	27%	67%	75%
Accuracy	50%	64%	87%

Graph 8.5 Histogram displaying range of exercise times for 119 men and women with ESRF felt suitable for renal transplantation



- Men: Number = 80, Mean =7.28 minutes, SD = 2.54 minutes
- Women: Number = 39, Mean = 5.77 minutes, SD = 2.59 minutes

Chapter 9

Left Ventricular Abnormalities, Coronary Artery Disease and Outcome in patients awaiting Renal Transplant

9.1 Introduction

The annual mortality rate of patient's waitlisted for renal transplant is 2.6 times lower than patients with ESRF not felt suitable for transplant and 1.7 times higher than patients with a functioning renal allograft (1). In an observational study of 604 wait-listed patients in Canada, Gill *et al.* found the annual CV event rate was 12.7% per year for diabetics and 4.5% per year for non-diabetics whereas the corresponding mortality rate was 3.4% and 1.2% per year respectively (13). Thus, CV morbidity and mortality for waitlisted patients is still 10 times that of the general population and CVD is responsible for 50% of deaths in the first 5 years after renal transplant.

Several factors affect prognosis, both whilst waiting for renal transplant and post-transplantation. Increased age and a history of diabetes identifies patients at higher risk of CV morbidity and mortality and these factors, along with a history of previous IHD or other vascular disease, help identify those patients who should have careful assessment for underlying CVD. In an effort to minimise the impact of CVD on survival after renal transplantation, guidelines exist for CV screening of transplant candidates to identify those patients at higher CV risk (34,243-244). Thus, theoretically, treatment can be instigated to minimise risk prior to transplant or the patient is excluded from the waiting list if estimated prognosis is very poor (e.g. severe, irreversible LVSD). However, whilst

following the screening guidelines, which focus mainly on the identification of CAD, can identify patients with obstructive CAD, there are no clear guidelines regarding the need for assessment of resting LV abnormalities and there is no clear consensus regarding how often CV screening should be carried out whilst patients remain on the waiting list. This is despite evidence from longitudinal observational studies that LV abnormalities are strong predictors of outcome both in patients on RRT and in patients who have undergone renal transplantation and that LV abnormalities progress with time.

McGregor *et al.* (86) studied 67 patients prior to renal transplant between 1988 and 1990 and found that LV mass and LV systolic function predicted post transplant outcome. In the more recent study by Sharma *et al.* (87), 203 patients underwent echocardiography prior to transplant between 1996 and 2001. Echocardiographic findings of LV posterior wall thickness ($p=0.014$, $\beta=1.06$), LV ESD ($p=0.002$, $\beta=3.03$), and the presence of mitral valve annular calcification ($p=0.036$, $\beta=2.71$) all predicted poorer outcome and a greater risk of CV events after transplant.

In view of the association of LV abnormalities and CAD with outcome in this population a combined, preferably non-invasive, screening test that accurately assesses both LV structure and function and the degree of underlying ischaemia is required and ideally such a non-invasive test should also give information regarding prognosis. Recently the work of Sharma *et al.* (33) reported an improved sensitivity and specificity of DSE to detect underlying significant CAD and resting LV abnormalities in a group of 125 renal transplant candidates. The results of DSE were compared to QCA and DSE was found to have a sensitivity of 88% and a specificity of 94% for the detection of a coronary artery stenosis of >70%. However, as previously discussed in Chapter 8, other studies assessing

the use of DSE in this population have not shown such a high accuracy based on the previously discussed arguments regarding both the visualisation of the LV and the calculation LV mass and function using echocardiography. We therefore aimed to determine whether CMR measurements of LV anatomy and function in this population were predictive of outcome and whether other positive findings such as the presence of LGCE or a high BNP level added additional prognostic information.

9.2 Methods

9.2.1 Subjects and Procedure

The 148 patients who were screened for the initial study were followed up yearly and details of outcome (all cause mortality) recorded via the West of Scotland renal database for a total of 4 years from the date of the initial CMR scan. Details regarding date of death were recorded and if the patients underwent renal transplantation, date of transplant. Follow-up ended in April 2007.

9.2.2 Statistics

Statistical analysis was performed using SPSS Version 14 software (SPSS inc. Chicago IL, USA). Baseline data are expressed as mean +/- SD or median, if not normally distributed. Differences between the groups were assessed using a two-sample t test (normally distributed data) or Mann Whitney U test (nonparametric data). The 95% confidence intervals for differences between groups in mean percentage change from baseline are given. Univariate predictors of outcome were identified using the Pearson chi-squared test with continuity correction. A p-value of less than 0.05 was considered significant. Independent predictors of outcome were identified using a Cox proportional hazards model using a multivariate stepwise paradigm. In addition a 3 step modelling procedure was performed with variables included in the model in the same order as in clinical practice. Firstly, only baseline demographic data was entered, followed by cine CMR results and finally results of LGCE imaging were added. The Kaplan Meier method was used to construct survival curves for compared groups of patients and the curves displayed with corresponding log rank statistics.

9.3 Results

9.3.1 Baseline follow-up

Patients were followed up for a mean of 50 months +/-18.8 months and 2 patients were lost to follow up (both patients moved to another city and transplant centre). During the follow up period a total of 39 patients died (26.4% of total cohort) before renal transplantation. A further 39 patients underwent transplantation, making up 35.1% of surviving patients and of the patients who received renal transplant, 5.1% have since died (2 patients). The remaining 68 patients were alive and on RRT at the end of follow-up. Mortality rate for the whole cohort was 5.3% per year and when this was split into diabetic and non-diabetic groups the annual mortality rate for diabetic patients was 10.4% per year and for non-diabetics was 4.2% per year.

9.3.2 Baseline characteristics of transplanted patients

The baseline demographics of patients who had received a renal transplant during follow-up were initially compared to those of surviving patients on RRT to examine any potential differences and are shown in Table 9.1. The only significant difference found between patients remaining on RRT at the end of the follow-up period and those with a functioning renal allograft was the number of previous transplants the patients had previously received. Of those patients who remained waitlisted on RRT, 29% had a history of previous failed renal transplantation whereas only 7.7% of patients with a transplant at the end of follow up had previously been transplanted (p=0.007).

Baseline demographics of the transplanted patients were then compared to those of patients who died during follow-up (Table 9.1). Transplanted patients were significantly

younger (46+/-11.7 years vs. 55+/-8.9 years, p=0.021) than those who had died and had a lower prevalence of IHD (12.8% vs. 37.8%, p=0.043) and diabetes (17.9% vs. 35.1%, p=0.046). Patients who died also had a significantly lower haemoglobin level compared to patients who were eventually transplanted (10.9+/-1.5g/dL vs. 11.8+/-1.6g/dL, p=0.039).

9.3.3 Baseline characteristics of patients who died during follow-up

The baseline demographics of the 39 patients who died during follow-up are displayed in Table 9.1. Initial comparisons were made with both patients who remained on RRT during follow-up and those who received a renal transplant. Compared to those who remained on RRT, patients who died had a shorter period of diagnosed renal failure 7.4+/-8 years vs. 9.5+/-8 years, p=0.035) and had been on RRT for a shorter period of time (24.9+/-26 months vs. 36.8+/-32 months, p=0.035). They were also less likely to have had a previous renal transplant (10.8% vs. 29.0%, p=0.042) and had a higher prevalence of IHD (37.8% vs. 13.0%, p=0.23) diabetes (35.1% vs. 10.1%, p=0.31) and other vascular disease (13.5% vs. 2.9%, p=0.48).

9.3.4 LV abnormalities and survival

LV measurements of mass, function and volumes for the group of patients who died during follow-up along with the corresponding results for those who remained on RRT and those who received a renal transplant are displayed in Table 9.2. A significantly higher proportion of patients who died were found to have LVSD (29.7%) compared to either those remaining on RRT (11.1%, p=0.035) or those who underwent transplantation

(10.3%, p=0.030). Patients who died also had a significantly higher ESV than the other two groups. Although patients who died had a higher mean LVMI and EDV than the other groups and a higher overall prevalence of LVH and LVDil these differences did not reach statistical significance.

The survival curves for patients with and without LV abnormalities are displayed in Graphs 9.1-9.4. Again, the log-rank statistics indicated that patients with high ESV (p=0.005) and LVSD (p=0.002) had a significantly higher mortality rate than those who survived and remained on RRT. Patients who died had a higher prevalence of a dilated EDV but this just failed to reach statistical significance (p=0.052). There was no significant increase in mortality conferred by concentric LVH in this cohort (p=0.645) and no significant increase in mortality in those that fulfilled the criteria for concentric remodelling (p=0.189). Furthermore, there was no overall significant difference in survival between patients who had a normal LV and all those with an abnormal LV at baseline (p=0.543).

The survival curves for different types of uraemic cardiomyopathy are shown in Graph 9.5. Patients with LVSD had worst overall survival followed by patients categorised as having eccentric LVH. Patients with normal ventricles had the best outcome.

9.3.5 Univariate predictors of outcome for total cohort

Patients who were alive at the end of follow-up and still on RRT were compared to those who had died during follow-up to identify univariate predictors of mortality in this population. Patients who underwent transplant during follow-up were censored from this analysis at the point of transplant. Univariate predictors of outcome are displayed in

Table 9.3. From baseline demographics, age (p=0.001), a shorter length of time on RRT (p=0.046) and a previous transplant (p=0.023) were significant univariate predictors of death. A history of diabetes (p=0.001), IHD (p=0.002) and all other forms of vascular disease were univariate predictors, as was a history of hyperlipidaemia (p=0.004).

With regard to non-invasive investigations, a finding of LVSD (p=0.010) or a high ESV (p=0.008) on CMR scanning were univariate predictors of death, as was a finding of ST changes on either the ECG (p=0.022) or ETT (p=0.018) and length of exercise time on ETT (p=0.006) was also significant. Finally, with regard to haematological and biochemical results, a low haemoglobin (p=0.017), high BNP (p<0.001) and a high blood glucose level (p=0.004) were all significant univariate predictors of death.

9.3.6 Multivariate predictors of outcome for total cohort

Variables which showed significance on univariate testing were combined in Cox proportional hazards model using a multivariate stepwise paradigm and the independent predictors of outcome are shown in Table 9.3 along with corresponding hazard ratios and 95% confidence intervals for the hazard ratios. After the baseline factors of age and a history of IHD or diabetes were corrected for, the majority of the other univariate predictors were not found to be significantly different between patients who died during follow-up and those who remained on RRT. Abnormal findings using CMR, ECG and ETT all lost significance, as did differences in drug therapy, haemoglobin value and glucose level. Apart from older age (p<0.001), a history of IHD (p=0.008) or diabetes (p=0.001), the only other independent predictor of death was serum BNP (p=0.015).

9.3.7 Influence of progression of LV abnormalities on outcome

Over half the initial cohort (57%, 84 patients) had a follow-up CMR scan at least 6 months after initial screening. The influence of progression and regression of LV abnormalities was examined to ascertain whether progression of LV abnormalities had any additional impact on outcome. Patients who showed more then 10% progression of LV mass, ESV, EDV or more than a 10% decrease in EF between scans were analysed compared to those who showed no change or regression of LV parameters during the study. There were no significant differences found for any LV parameter and on univariate testing, progression of uraemic cardiomyopathy or development of concentric LVH over a mean period of 8 months did not impact on outcome for the cohort.

9.3.8 Influence of coronary artery disease on outcome

The outcome of patients with severe CAD compared to those with mild or no CAD was significantly lower on Kaplan Meier analysis (p=0.032) (Graph 9.6). Although the group of patients who underwent coronary angiography was relatively small (38 patients), those who were found to have a significant stenosis of one or more epicardial coronary arteries they were significantly more likely to die during follow-up than those who did not have a significant coronary stenosis (p=0.032). When the results of coronary angiography were added in as a step in the multivariate model, QCA was not found to add independent weight to the model with regard to predicting outcome.

9.3.9 Influence of late gadolinium contrast enhancement on outcome

A smaller proportion of patients in the cohort (40%, 60 patients) underwent CMR scanning before and after the administration of a gadolinium based contrast agent. Patients who displayed LGCE were compared to those who received gadolinium and did not display LGCE. Both the presence of any pattern of LGCE (p=0.019) and the specific subendocardial pattern suggestive of IHD (p=0.005) were significant univariate predictors of outcome. The diffuse pattern of LGCE by itself was not a significant univariate predictor of outcome (p=0.058).

Survival curves for patients with and without LGCE and type of LGCE are displayed in Graph 9.7. The corresponding log rank statistics were significant for the discrete pattern of LGCE consistent with ICM (p=0.005) but not for the pattern of diffuse LGCE consistent with hypertrophic cardiomyopathy (p=0.245).

However, when the presence of LGCE was included in the model along with age, a history of IHD and a history of diabetes neither the presence of any LGCE or the subendocardial pattern of LGCE were found to be independent predictors of outcome for the cohort.

9.4 Discussion

Previous echocardiographic studies examining LV abnormalities in patients prior to renal transplantation have found that particular LV abnormalities identified pre-transplant, predict both CV and all cause mortality post-transplant. Whilst is has also been established that abnormal ventricular anatomy or function also has a significant impact on outcome in patients on RRT, relatively little is known about the impact of LV abnormalities in the subgroup of patients on RRT awaiting renal transplantation. As waiting time for renal transplantation continues to increase, management of patients on the waiting list becomes more important in an effort to minimise progression of CVD.

In contrast to the studies of McGregor *et al.* (86) and Sharma *et al.* (87) we did not find that LV abnormalities, identified using CMR, independently predicted poorer outcome although LVEF and LV ESV both showed significance on univariate testing and with Kaplan Meier survival analysis. In the study of McGregor *et al.* (86) ESV and LV function measured by Fractional Shortening were found to independently predict survival. However, although age was used in the Cox regression analysis model, a history of IHD and diabetes were not. Similarly, in the study of Sharma *et al.* (87) LV ESD and posterior LV wall thickness were found to be independent predictors of mortality post-transplant. Age again was an independent predictor of mortality but whilst a history of IHD was significant on univariate testing ($p=0.04$) it was not found to be an independent predictor of mortality and a history of diabetes was not significant even on univariate testing. The reasons for this are not clear but it is notable that only 4% of the total cohort had a history of IHD whereas 42% of the cohort had a history of diabetes. This suggests the cohort of Sharma *et al.* was an extremely highly selected population or alternatively

that the prevalence of identified IHD pre-screening was falsely low. Thus in the case of both studies the presence of LV abnormalities may have actually been a marker for underlying and previously undiagnosed CAD.

In previous chapters of this thesis we have found that LV abnormalities, especially a high ESV and low EF, are closely associated with a history of IHD. Once IHD and diabetes were factored into multivariate analysis along with age, the results of all non-invasive tests, namely CMR findings, ECG ST abnormalities and ETT time lost significance. Similarly, although the presence of a discrete pattern of LGCE, suggesting ICM, was a univariate predictor of outcome this too was not found to be an independent predictor of outcome, after diabetes and a history of IHD were included in the multivariate model.

Patients who died whilst waiting for transplant had, on average, a shorter period of renal failure and time on RRT than patients surviving without transplant at the end of the study and it is likely that this reflects bias created by survival effect in those remaining on RRT. It is also unsurprising that patients undergoing renal transplantation were less likely to have had a previous transplant due to screening prior to transplant and the greater likelihood of cross-reactive antibodies in patients who have previously received a renal allograft. However, in contrast to previous studies (11) this was the only difference observed between patients who received a transplant during the study and those remaining on RRT at the end of the study. There was no difference in age, and diabetic patients, as well as those with a history of IHD, were equally as likely to receive a transplant as to remain on RRT, suggesting a well selected group of transplant candidates. Whereas 39 patients died whilst on RRT, only 2 patients died post transplant during follow-up. These deaths were both in the first year post transplant, one was the oldest

patient in the cohort at 70 years of age and the other was a diabetic with a history of IHD. Again, although numbers are too small to carry out any meaningful analysis on patients post transplant, the three features of advancing age, diabetes and a history of IHD all feature in the patients who died after transplant. Although on the basis of risk stratification both these patients were high risk, it is very difficult to exclude patients from waiting lists unless prognosis is felt to be very poor as previous studies have shown that individual life expectancy is increased on average to 3 times that of remaining on RRT without transplant, even for higher risk patients (3).

It is also notable that a much larger proportion of patients died whilst waiting for renal transplant than died after transplant. Whilst some of this is undoubtedly due to the mortality benefit of transplantation and the potential negative impact on survival of remaining on the waiting list for a prolonged period of time, it is likely that a proportion of patients who were screened during the study did not gain access to the transplant waiting list for reasons other than CVD, which may have skewed the results and several patients died before decision regarding placement on the waiting list was made.

With a predictive model of age over 60 years, a history of diabetes and a history of IHD the sensitivity of predicting death was 80% and the specificity 51%. With the addition of a high BNP level to the model, the sensitivity remained at 80% but the specificity improved to 81%. This suggests that the addition of BNP to the model significantly decreased the number false negative results, in other words helped identify which patients outwith the initial model had a poorer prognosis. This is the first study to suggest that BNP level can independently predict outcome for patients felt suitable for renal transplantation and was a more powerful predictor than any of the other non-invasive

tests in this cohort. It is well recognised that elevated levels of biomarkers such as the natriuretic peptides predict outcome in patients with normal renal function after AMI and in those with LVSD and is useful in monitoring treatment of heart failure. With regard to patients with renal dysfunction, previously Malamacci *et al.* (139) studied BNP levels in 246 patients with ESRF (212 on haemodialysis and 34 on PD) and patients with a history of CHF or LVSD were excluded. The study found BNP to be predictive of both CV and all cause mortality after 26+/-10 months of follow up, independent of echocardiographic findings.

In a more recent study Madsen *et al.* (289) studied the use of NT-proBNP in 109 patients on haemodialysis. Similarly to BNP in our study and in other echocardiographic studies, NT-proBNP correlated more strongly with LV mass than LVEF in patients with ESRF and on multivariate analysis age and NT-proBNP level were found to be the only independent predictors of outcome. Patients with IHD and CHF were included in this study and 34% of the cohort was diabetic. Although we found the determinants of BNP in Chapter 5 to be LV mass and LV EF, the higher levels and range mean that BNP will not be as accurate in diagnosing LV abnormalities in patients with renal failure as it has been in patients with normal renal function. However, the ability of BNP to predict outcome in this population means it may become a useful adjunct in the renal transplant assessment clinic for decisions regarding the need for more aggressive investigation such as coronary angiography in this population.

Unlike previous studies in patients with ESRF, we did not find concentric LVH to be predictive of outcome. Although the survival curves had separated by the end of the study for those with LVH and those with normal ventricles, this did not reach statistical

significance. Again, other factors in this fitter population of patients compared to those in the general dialysis pool may have affected the results or reflect the fact that patients with concentric LVH are earlier in the course of evolution of CVD than those with a dilated LV or with LVSD. Similarly, although we found with follow-up that progression of LV abnormalities was mainly via progression of LVH in the relatively short follow-up time of 8 months, we did not find that either an increase in LVMI over this period of time or the development of new LVH impacted adversely on outcome. Patients with a dilated LV or LVSD did not show further significant progression by the follow up CMR scan, although the tendency in patients with a low EF was continued adverse remodelling. Furthermore, although previous authors studying populations with essential hypertension had identified a further type of LV geometric pattern with adverse outcome we found no such association in this cohort

The findings of this study are supportive of those of Gill *et al.* (13) who observed in 604 patients that a risk stratification system based on age, diabetes and a history of IHD was better at predicting CV outcome both whilst patients remained on the waiting list and in the first 12 months post transplant than any combination of ECG, ETT, echocardiography and MIBI and also found that repeat surveillance with non-invasive imaging did not predict outcome either.

However, the sensitivity and specificity of our model using risk stratification on the basis of age and co morbidity along with serum BNP only gave a specificity and sensitivity of 81% and 80% respectively, which although is at the level generally accepted for a screening test does leave room for improvement and in combination with another form of

functional stress imaging such as adenosine or dobutamine stress CMR may improve the overall accuracy with regard to predicting prognosis in this population.

Although several studies have advocated that only coronary angiography is predictive of post transplant AMI and CV death, when high risk patients such as diabetics are screened with invasive coronary angiography over half do not have significant CAD and only a small proportion, in the region of 10-12% have CAD that is treated with surgery or PCI (290). Thus, with this strategy, many unnecessary angiograms are performed that are not without undue risk.

In this population of 148 patients felt suitable for renal transplantation we have found that a careful clinical assessment for symptoms or history of IHD along with advancing age, a history of diabetes and an elevated level of BNP was a strong predictive model for adverse outcome. However, newer functional non-invasive imaging modalities may improve the accuracy of this model and decrease the number of patients subjected to diagnostic coronary angiography, simply for risk stratification. Further studies targeting the usefulness of BNP in deciding which patients need an invasive investigation strategy are required as well as investigation of other non-invasive techniques in efforts to improve the detection of underlying CAD, which in this study was found to be a stronger predictor of outcome than concentric hypertrophic cardiomyopathy, in patients undergoing assessment for renal transplantation.

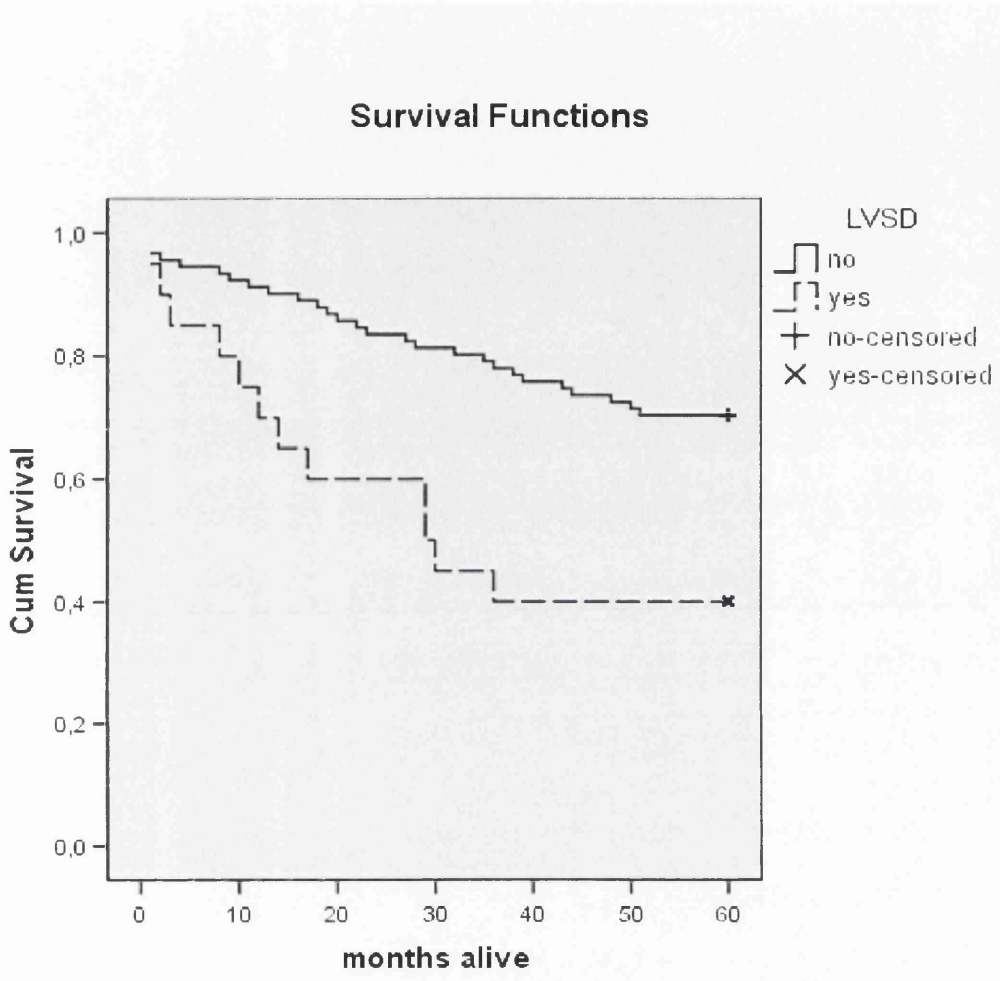
Table 9.1 Baseline demographics of surviving patients who remained on RRT, those who received a renal transplant and those who had died by end of follow-up period. (*-RRT vs. Transplant, $p<0.05$; **-RRT vs. dead, $p<0.05$; #-Transplant vs. dead, $p<0.05$)

Baseline Variable	***RRT*** ***n=68***	***Transplant*** ***n=39***	***Dead*** ***n=39***
Age (years)	50+/-9.2	46+/-11.7	55+/-8.9**#
Sex (%male)	71	69	62
Patients on haemodialysis (%)	62	65	51
Length of time on RRT (months)	36.8+/-32	28.6+/-25	24.9+/-26
Length of renal failure (yrs)	9.5+/-8	8.2+/-9	7.4+/-8**
Previous renal transplant (%)	29.0	7.7*	10.8**
History of IHD (%)	13.0	12.8	37.8**#
Previous AMI (%)	5.8	7.7	18.9**
History of CHF (%)	4.3	7.7	13.5
Diabetic (%)	10.1	17.9	35.1**#
History of hypertension (%)	97.0	87.2	97.3
History of hyperlipidaemia (%)	26.1	35.9	54.1
Current smoker (%)	30.9	25.6	29.7
Family history of IHD (%)	22.1	28.2	32.4**#
Peripheral vascular disease (%)	2.9	2.6	13.5**
Systolic BP (mmHg)	137+/-24	135+/-25	134+/-24
Diastolic BP (mmHg)	81+/-12	80+/-12	77+/-11
Cholesterol level (mmol/L)	5.7+/-1.8	5.8+/-1.8	5.2+/-1.2
Haemoglobin (g/dL)	11.8+/-1.5	11.8+/-1.6	10.9+/-1.5#

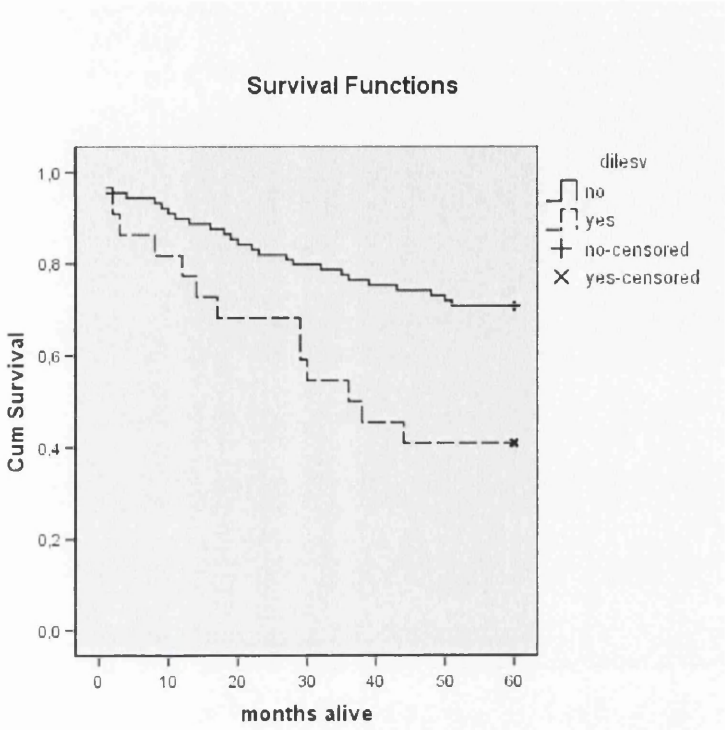
Table 9.2 Differences in LV parameters between patients who remained on RRT, those who received a renal transplant and those who died during follow-up. (*-RRT vs. dead, $p<0.05$); #-Transplant vs. dead, $p<0.05$)

PARAMETER	*RRT n=68*	*Transplant n=39*	*Dead n=39*
LVEF (%)	67+/-11	66+/-10	60+/-17
LVSD (%)	11.1	10.3	29.7*#
LVMI	104(+/-33.2)g/m²	101(+/-36.3)g/m²	111(+/-36.7) g/m²
LVH (%)	72.2	59.0	78.4
LVEDV	74(+/-26.1)ml/m²	76(+/-31.4)ml/m²	84(+/-35.4)ml/m²
LVESV	25(+/-17.8) ml/m²	25(+/-17.9)ml/m²	36(+/-33.4)ml/m²#
DilLV (%)	12.5	17.9	24.3
Normal LV (%)	27.8	35.9	21.6
Concentric remodelling (%)	8.3	12.8	16.2

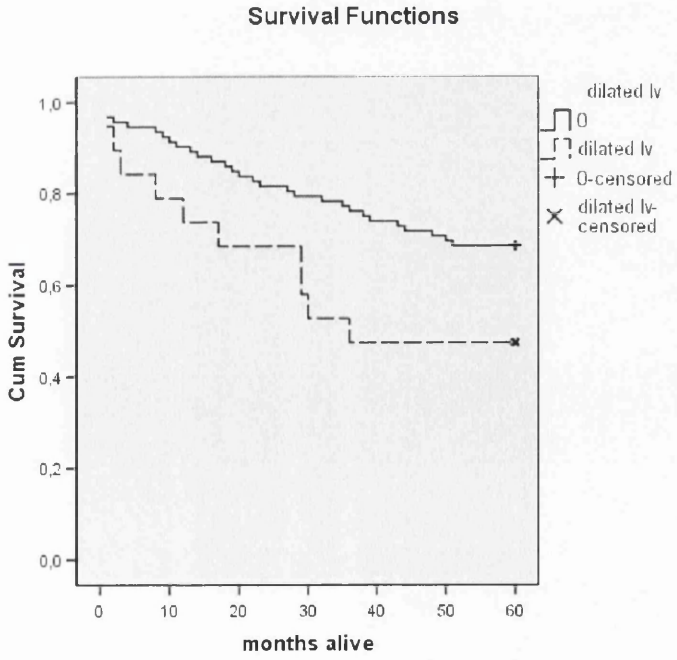
Graph 9.1 Kaplan-Meier survival curve displaying outcome for patients with and without LVSD (Log-rank statistic, p =0.002)



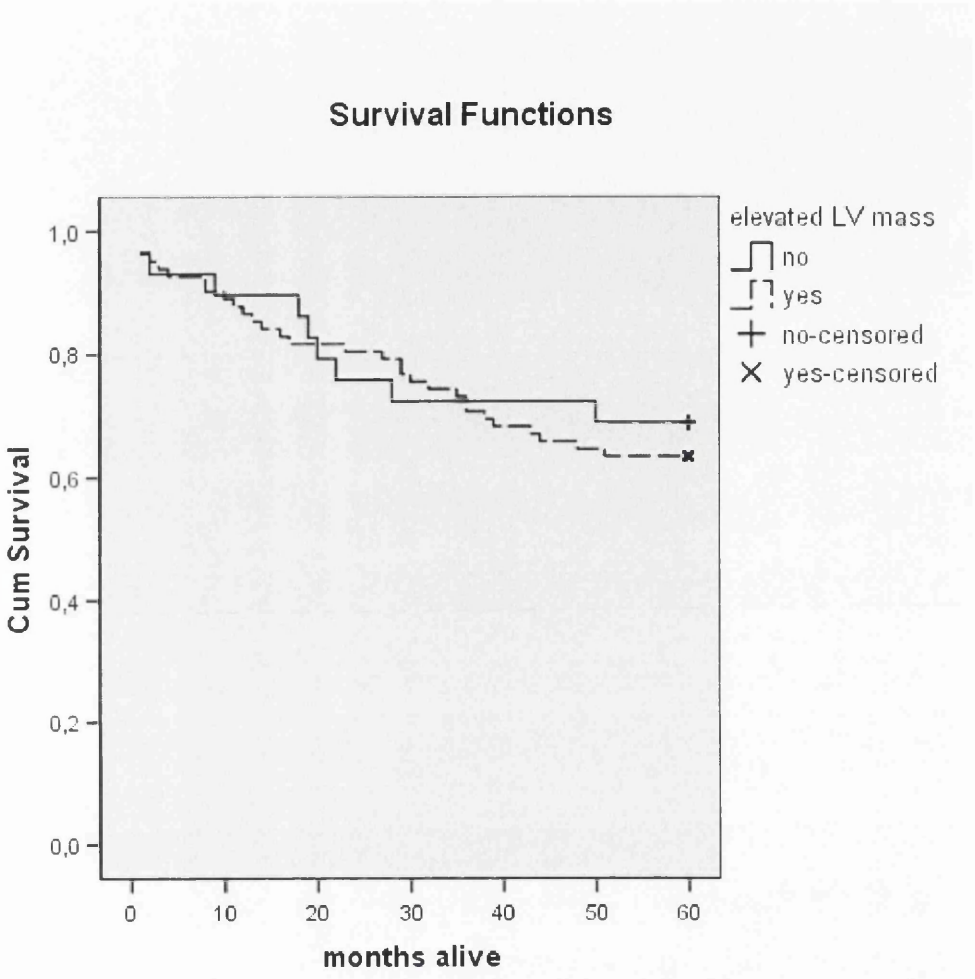
Graph 9.2 Kaplan-Meier survival curve displaying outcome for patients with and without elevated ESV (Log-rank statistic, p=0.005)



Graph 9.3 Kaplan-Meier survival curve displaying outcome for patients with and without elevated EDV (Log-rank statistic, p=0.052)



Graph 9.4 Kaplan-Meier survival curve displaying outcome for patients with and without concentric LVH (Log-rank statistic, p=0.645)



Graph 9.5 Kaplan-Meier survival curve displaying outcome for patients with different types of cardiomyopathy categorised by CMR (Log-rank statistic, p=0.012)

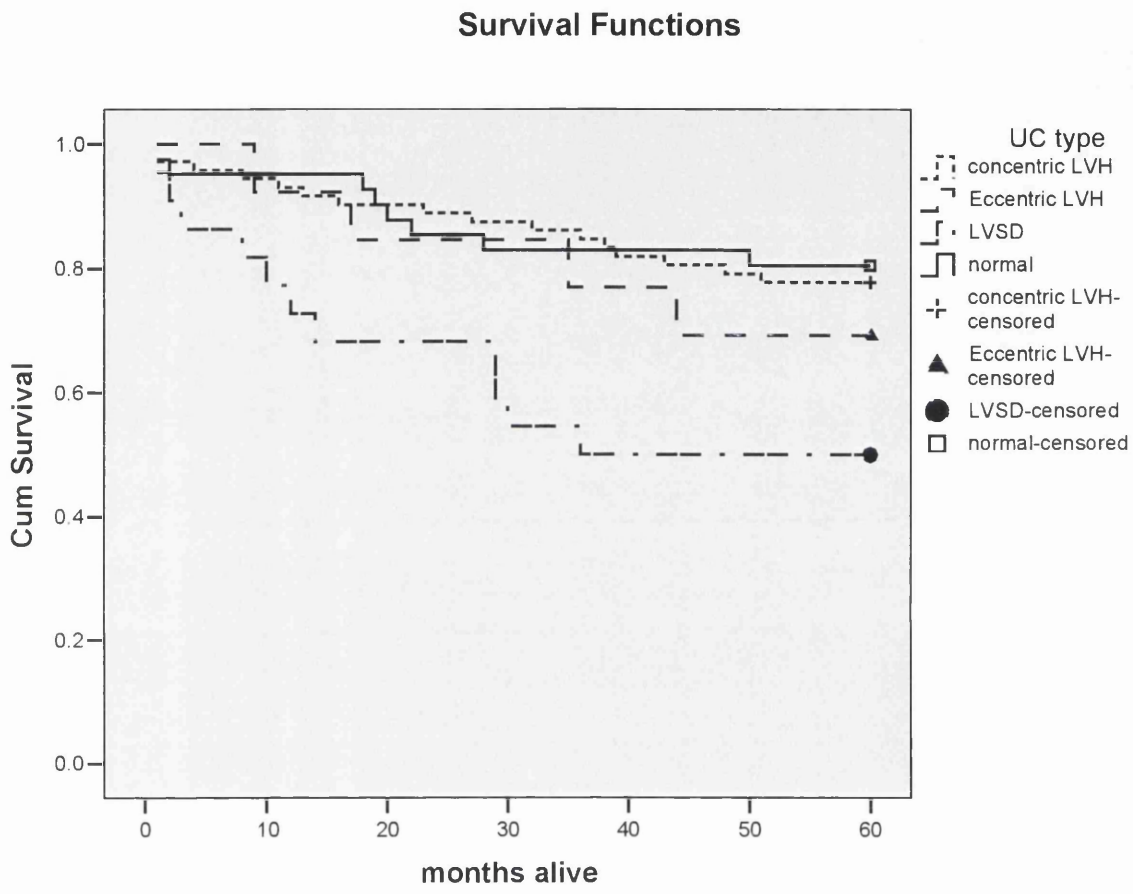
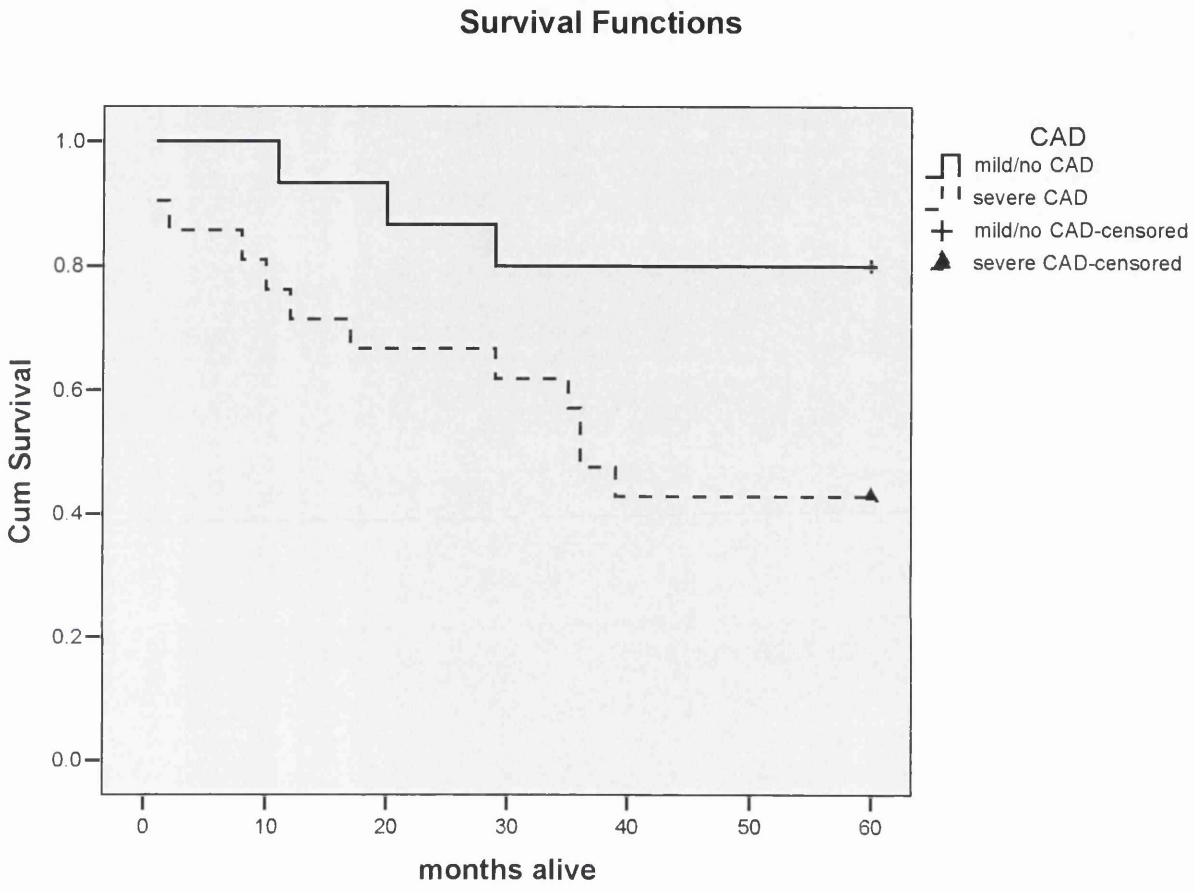


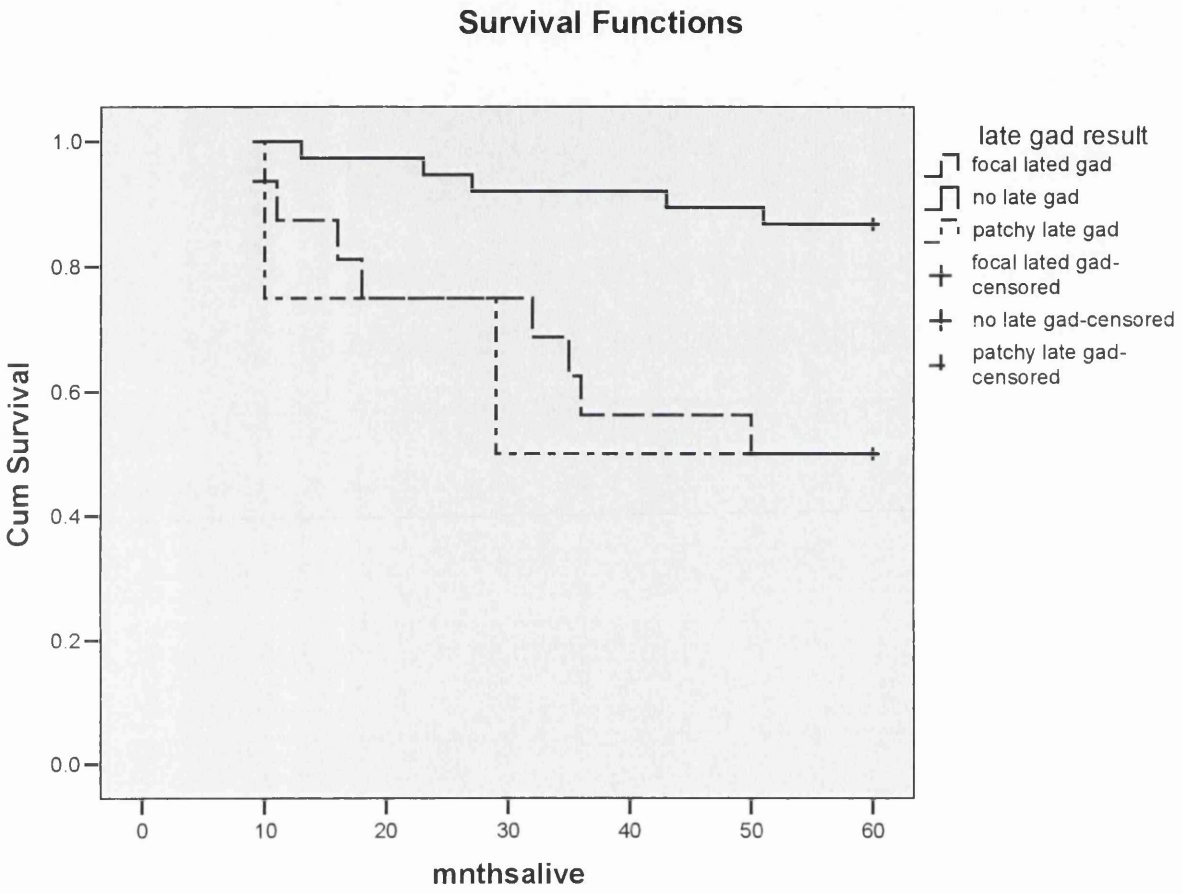
Table 9.3 Univariate and multivariate predictors of death in cohort

Univariate predictor	***p-value***	***Multivariate predictor***	***Hazard Ratio (95% CI)***
Age	p=0.001	p<0.001	1.168 (1.088-1.254)
Length of time on RRT	p=0.046	NS	
History of previous transplant	p=0.023	NS	
History of IHD	p=0.002	p=0.002	7.162 (2.016-25.444)
History of diabetes	p=0.001	p=0.001	10.264 (2.513-41.925)
History of CVA	p=0.004	NS	
History of PVD	p=0.017	NS	
History of hyperlipidaemia	p=0.004	NS	
LVSD	p=0.010	NS	
High ESV	p=0.008	NS	
ST changes on ECG	p=0.022	NS	
ETT time	p=0.006	NS	
ST changes on ETT	p=0.018	NS	
Presence of LGCE	p=0.005	NS	
Haemoglobin	p=0.017	NS	
BNP	p<0.001	p=0.001	3.414 (1.199-9.719)
Glucose level	p=0.004	NS	

Table 9.6 Kaplan-Meier survival curve displaying outcome for patients with and without severe CAD at QCA (Log-rank statistic, p=0.032)



Graph 9.7 Kaplan-Meier survival curve displaying outcome for patients with patchy LGCE, discrete LGCE and no LGCE on CMR scan (Log-rank statistic, p=0.005)



Chapter 10

Discussion

10.1 Principle Findings of the Study

LVH is a potent marker of CV risk in the general population and those with essential hypertension, as documented in several longitudinal studies (291-294). Several factors explain this close link. The predictive power of LVH is due to the fact that it is both a marker of vascular abnormalities, such as hypertension and increased arterial stiffness and a causal risk factor by itself as it influences coronary haemodynamics and myocardial oxygen requirement. Furthermore, in the evolution of CVD from the exposure to causal risk factors to the clinical manifestations of overt disease, LVH occupies a central position as it is already a marker of the impending CVD when it is not yet clinically evident. Thus, as compared with causal risk factors, such as hypertension and diabetes, LVH identifies a condition of disease which is closer to the end of the natural evolution of CVD and LVH itself also directly accelerates this evolution.

It is therefore unsurprising that LVH has also been shown to be a strong predictor of CV outcome in patients with CRF and the prevalence of LVH described using echocardiography in patients with progressive renal failure not requiring RRT is similar to that observed patients with essential hypertension. Studies of patients with CRF have estimated that between 27-40% have LVH, depending on GFR (42) and in patients with essential hypertension the prevalence is between 28-50%, depending on age and sex (78,295). As the prevalence of hypertension in patients prior to RRT is around 80% (38-

39), it may be more appropriate to compare patients with CRF to those with essential hypertension, rather than the general population when discussing LV abnormalities.

It is only once patients require RRT that the prevalence of LVH and LV dilation dramatically increases above that of patients with essential hypertension (69), in line with the point on the renal timeline that is most associated with haemodynamic overload and therefore, also most associated with a volume dependant increase in the diameter of the LV. One of the major findings of this study is that the proportion of patients with a dilated ventricle, measured using CMR, was dramatically lower than that previously documented using echocardiography. Whereas a total of 16.2% of the cohort were found to have a dilated LV, only 6.1% were observed to have eccentric LVH whereas the other 10.1% had associated LVSD. Other echocardiographic studies in patients with ESRF selected for transplant have found a prevalence of between 20%-80% for LV dilation (86-87) and in the studies of Foley *et al.* (69), 28% of patients on RRT were found to have eccentric LVH. CMR is a direct method of measurement of LV structure and function, not dependant on geometric assumptions and therefore it is less dependant on loading conditions than echocardiography. The findings of this study support evidence from previous studies, of both patients with essential hypertension (296) and those with ESRF (202), in which the use of M-mode echocardiography was found to overestimate LV abnormalities, especially LVMI, compared to CMR. The calculation of LVMI is dependant on cubing the measurement of LVIDD and therefore, if a ventricle is volume loaded, the calculation of both LV volumes and mass will be falsely high (194-195). Overestimation of both LV mass and volume may partly explain the much higher

prevalence of LV abnormalities in patients with ESRF compared to either those patients who are in the pre-dialysis stages of progressive renal failure or patients post transplant.

Another major finding of this study was the observed close relationship between LV dilation, LVSD and IHD. The determinants of LVSD and ESV were identified as IHD and diabetes and the prevalence of IHD progressively increased from 11.3% in patients with concentric LVH, to 27.3% in those with a dilated LV and finally to 45.5% in those with LVSD. As expected, EDV was more dependant on loading conditions than ESV and displayed a relationship with both haemodialysis as type of dialysis therapy and diastolic BP but ESV showed no such relationship. A close relationship between LV dilation, LVSD and IHD was also observed in Chapter 8. All patients with LVSD who received a gadolinium based contrast agent displayed a pattern of LGCE typical of previous AMI and whereas 42% of patients displaying a pattern of LGCE typical of ICM had a dilated LV, only 4.7% of patients found to have no LGCE had elevated ventricular volumes. Previously, echocardiographic studies have found a strong relationship between LVSD and a history of IHD but a much weaker relationship between LV dilation and IHD (71). Such studies have observed stronger associations between LV dilation and factors exacerbating haemodynamic overload such as anaemia, hypoalbuminaemia and haemodialysis (17,71) and once again, using a loading independent method of measurement has revealed a stronger association with IHD and a much weaker association of LV dilation with markers of increased haemodynamic load.

As in previous echocardiographic studies (69,75-76), concentric LVH was found to be the dominant type of cardiomyopathy in this study and 50% of the total cohort were observed to have elevated LV mass in the context of normal LV volume. This pattern of

LVH was associated with markers of pressure and volume overload, namely BP and type of dialysis therapy and unlike those with a dilated or poorly functioning LV, was not directly associated with IHD. However, patients with severe CAD at angiography had a higher mean LVMI compared to those with mild CAD or normal coronary arteries, suggesting that concentric LVH does have a relationship with CAD but that LVH may occur earlier in the evolution of CAD and CVD, whereas LV dilation and LVSD occur later.

Therefore, rather than the three types of uraemic cardiomyopathy proposed by Foley *et al.* (Figure 1.1) (69) in previous echocardiographic studies, we propose that the two major types of cardiomyopathy in patients with ESRF are concentric hypertrophic cardiomyopathy and ischaemic cardiomyopathy with a much smaller contribution from eccentric cardiomyopathy than previously thought and a much closer association of LV dilation with IHD, when a load independent method of measurement is used to identify and quantify LV mass, volumes and function.

This proposed pattern again shows similarities to studies in patients with essential hypertension. Although the natural pattern in essential hypertension is concentric LVH, this may not always be recognised as many patients also have underlying CAD which causes the myocardium to remodel to a more eccentric or dilated pattern. These patients therefore present with eccentric LVH and systolic dysfunction and this has been found in several studies of patients with essential hypertension including those using the Framingham cohort (297) and the LIFE study (257). The major evolutionary pattern of uraemic cardiomyopathy in patients with progressive renal failure is also concentric LVH and concentric LVH is found early in the course of CRF in association with hypertension

and arterial stiffening (42). It is only in the later stages of progressive renal failure that volume overload plays a more important role, often when concentric LVH is already established and therefore patients are already likely to have pre-clinical CVD, for which concentric LVH is a marker.

Although 29% of patients were found to have a normal LV at baseline screening, a surprising finding was the relatively rapid development of concentric LVH when patients returned for follow up 8 months after initial screening. Although overall, no significant differences in LV parameters were observed, 45% of patients with initially normal ventricles had developed concentric LVH by the time of follow up. The reasons for this were not clear and the group of affected patients was relatively small (13 patients) but this finding suggests that CV risk assessment and surveillance should continue after patients are listed for renal transplant, rather than simply undergoing a single 'gateway' assessment, even in those who are initially categorised as 'lower' risk.

In addition to the haemodynamic overload associated with renal failure, anaemia also affects cardiac loading conditions through adaptive physiological mechanisms including increased venous return and increased heart rate. Using a 'volume status independent' method of measurement for the calculation of LV mass we found in this study that although anaemia was associated with a higher CO and a higher EDV, no relationship was observed between haemoglobin level and LV mass. As discussed previously, the calculation of LV mass using M-mode echocardiographic measurements is highly dependent on the internal diameter of the LV and it therefore could be concluded that this dependence has led to the overestimation of the relationship between anaemia and LV mass in this population. This observation is important and if replicated in future studies

could lead to a move away from the continued and currently failing (107-108) attempts to prove regression of LVH is possible with treatment of anaemia, and instead a move toward concentrating on targeting regression of LVH via the control of BP. It is notable that erythropoietin was the most commonly prescribed drug in this cohort of patients whereas 33% of patients were not prescribed antihypertensive medication, despite the finding that 20% of these patients were hypertensive on the day of screening and in total, 51% of patients in the cohort were found to have hypertensive BP readings. Furthermore, in high risk subgroups such as diabetic patients and those with a history of IHD, 55.6% and 42.9% respectively were found to be hypertensive at screening.

The prescription of cardioprotective medication was generally low in this population of patients, even in the higher risk groups. Following the UK Renal Association guidelines (244-245), 108 patients of 148 in the cohort are categorised as 'high' risk and only around 40% of these patients were established on any form of cardioprotective medication. It is well recognised that the evidence for primary prevention of CVD using aspirin, statins and ACEI's is scant in patients with ESRF but in 1998 the National Kidney Foundation Task Force on CVD published a document detailing proposed guidelines for the future control of the 'epidemic' of CVD in patients with renal failure (247). This document stated that when managing CV risk in patients with CRF, although there was a lack of evidence for following the primary and secondary preventative strategies for CVD, established in the normal population, these guidelines should be applied to patients with CRF until more specific evidence was available. Furthermore, patients with CRF should be considered 'high risk' for the development of CVD and thus

primary preventative measures, such as statin therapy, should be applied to this population.

In addition to improvements in the treatment of standard CV risk factors such as hypertension and hyperlipidaemia (50% of the total cohort and 60% of diabetics had high total cholesterol at screening), improvements in the identification of those patients with previously undiagnosed or asymptomatic CAD are also required. Using CMR, in this study 11 (18.3%) patients out of the 60 investigated using a gadolinium based contrast agent showed evidence of previously unrecognised AMI and 6 of these patients had no previous history of IHD. CMR imaging using LGCE therefore identified a group of patients at higher CV risk and whilst echocardiography may have identified those with associated LVSD, the aetiology of the cardiomyopathy as ICM would not have been apparent. The accuracy of this resting non-invasive imaging investigation was also higher than either of the currently used methods of non-invasive stress testing employed in the West of Scotland, with an accuracy of 87% for the detection of severe CAD compared to 64% for stress perfusion imaging and only 50% for ETT. The sensitivity and specificity of SPECT imaging found in this study are similar to that from other studies investigating CAD in patients with ESRF (174) and it is likely that the high false positive rate and lower accuracy of this technique in patients with ESRF is due to additional perfusion abnormalities observed in patients with LVH (298).

With the use of CMR to quantify LV mass and function, we found that serum BNP correlated more strongly with LV mass and LVEF than previous echocardiographic studies (140). However, the accuracy of BNP to identify patients with LVSD was lower than that found when investigating the general population (122). Whilst the sensitivity of

BNP to detect LVSD in patients with ESRF was similar to that found for the general population (77% vs. 79%), the specificity of the test was lower (87% vs. 79%) and this translates into a lower NPV (95% vs. 90%). This decrease in overall accuracy is likely to reflect the higher levels of circulating BNP in patients with renal failure and the higher range of variability. It is also likely that the high prevalence of LVH in this population also has a confounding effect. Both this and previous echocardiographic studies have found LVMI to correlate more strongly with BNP than LVEF and the predominance of LVH in this population, including those with LVSD may explain this finding. The high prevalence of LVH in this population means that the pre-test probability of LVH is much higher than that of the general population which infers that the NPV of BNP to detect LV abnormalities in patients with renal failure will be lower. Studies assessing the utility of BNP to detect LV abnormalities in patients with essential hypertension have also found a lower sensitivity and specificity than that observed in the normal population. Nishikimi *et al.* (299) investigated the relationship between LV geometry and BNP in 90 patients with essential hypertension using echocardiography. The study found a prevalence of LVH of 63% in this population using M-mode echocardiographic criteria and found the sensitivity and specificity of BNP to detect LVH of 60% and 82% respectively, which is similar to the values we found for the detection of LVH in this study which were 63% and 79% respectively. Thus, although BNP is a more accurate method of detecting LV abnormalities than the resting ECG in this population, it is unlikely to be accurate enough to use as an alternative to echocardiography or CMR for the detection of LV abnormalities. However, a low BNP level does help exclude those patients who do not

have LVSD and a high BNP level was found to be an independent prognostic indicator in patients undergoing assessment for renal transplantation.

This implies that whereas a low BNP level does not rule out LV abnormalities such as LVH or LVDil, it is unlikely that the patient has LVSD and the prognosis for the patient is better than that of a patient with an elevated BNP. Thus BNP may have potential for the identification of high risk patients for whom more intensive risk assessment should be performed before placement on the waiting list. For patients with essential hypertension, aggressive control of BP and resultant regression of LVH result in lowering of BNP levels and the findings of our study certainly warrant the further investigation of the usefulness of BNP for patients undergoing assessment for renal transplant both to identify those at higher risk of death and as a possible means of monitoring prognosis in interventional trials targeting LVH in this population.

The survival of patients also depended on the type of uraemic cardiomyopathy identified using CMR. If LV abnormalities suggesting an underlying ICM were identified, that is, LV dilation or LVSD, outcome was poorer than those with a normal ventricle using Kaplan-Meier analysis. However, patients who were found to have concentric LVH did not have a significantly different outcome compared to those with normal ventricles and this is in contrast to previous echocardiographic studies. The reasons for this are unclear but may represent a highly selected population of patients suitable for renal transplant.

When the independent predictors of outcome in population were studied using a Cox regression model, LVDil and LVSD were not identified as independent predictors of outcome after age, a history of IHD and diabetes were included in the regression model. These findings once again are in contrast to previous studies of LV abnormalities in

patients with ESRF. In this study a history of IHD was defined as previously documented CAD, previous AMI or a previously abnormal stress test in combination with the prescription of anti-anginal medication. This is in contrast to previous studies in which a history of IHD was defined on the basis of clinical symptoms suggestive of angina in addition to previously documented CAD. It is well recognised that symptoms of chest pain especially in patients with LVH do not necessarily imply underlying significant CAD and the more strict definition of IHD that we used in this study may help explain the lack of influence of LVSD and LVDil on outcome once baseline factors were controlled for. It also should be noted that this study was not specifically powered to determine outcome so the results should be interpreted with caution.

Using an outcome model including age, diabetes and a history of IHD, adverse outcome was predicted with a sensitivity of 80% and a specificity of 51%. This implies that whereas this model is relatively useful for the detection of those patients at high risk, the low specificity means there will be an unacceptable number of false negatives. However, once the finding of a high BNP was added into the model the specificity increased to 81% with no change to the sensitivity of the model.

In conclusion, this study has defined the prevalence and determinants of LV abnormalities in a group of patients considered suitable for renal transplantation in the West of Scotland using CMR. Using a loading independent method of measuring LV volumes and mass and the technique of LGCE, a close association between LVSD, LVDil and CAD has been identified and a history of CAD in association with older age, diabetes and high BNP level is a strong predictor of outcome. The findings of this study suggest that the evolution, natural history and determinants of LV abnormalities in

patients with CRF may not be that different to the general population or other high risk patient groups, such as those with essential hypertension; rather CRF accelerates the same process.

CMR is a well tolerated and accurate method of assessing the uraemic heart. The high accuracy and reproducibility associated with this technique imply it is ideally equipped for use in future appropriately powered studies targeting both regression of LVH and the potential reverse remodelling of LVDil and LVSD in patients with progressive renal failure.

10.2 Strengths of the Study

The main strength of this study is the method of measurement used to identify and quantify LV abnormalities. The accuracy of CMR and resultant low range of variability means that studies of the LV using CMR of more than 60 patients are considered large. For example, in Chapter 5 we identified patients with initially normal ventricles who developed LVH with follow up and these patients on average gained 10g over the period between baseline and follow up scans. If an echocardiographic study was used to detect the same degree of change with a power of 90% and significance of $p<0.05$, then 4638 patients would have needed to be recruited (213).

The strict definitions of both IHD and CHF are also relative strengths of this study and may have contributed to a much closer association of LV abnormalities with CAD than previously documented in other studies and use of the detailed West of Scotland renal database, in which every patient referred to the renal unit is included, meant that no data

was missing regarding baseline demographics for the population and that mean measurements of haemoglobin level were used in the study rather than single values.

The long period of follow up is also a relative strength of this study. Although this study was not specifically powered to determine predictors of outcome, data on outcome and all cause mortality was collected yearly from the West of Scotland renal database and the use of the database also meant that all patients who underwent renal transplantation were easily identified and that very few patients were lost to follow-up.

10.3 Weaknesses of the Study

One weakness of this study is the lack of a direct comparison with echocardiography in the same patient group to prove there is a different pattern of uraemic cardiomyopathy when using CMR as the method of measurement as compared to echocardiography and a relationship between anaemia and echocardiographic measurements but not CMR measurements. However, previous work by our group has directly compared LV abnormalities in patients with ESRF using both echocardiography and CMR. Stewart *et al.* (202) studied 40 patients with ESRF on a post dialysis day using CMR and M-mode echocardiography. This study found that as the ventricular volume of the LV increased, echocardiography progressively overestimated LV mass compared to echocardiography and other studies have also found overestimation of LV mass when studying an abnormal LV using echocardiography. This study was designed as a preliminary study of the use of CMR in patients with ESRF to identify potential for future interventional trials targeting LV abnormalities and subsequent ongoing work within our group is now also directly comparing echocardiography and CMR. It should also be noted that one of the aims of

this study was to compare the use of CMR to the current practice for assessment of CV risk in patients undergoing assessment for renal transplant. Whilst assessment for underlying CAD is relatively routine, the use of echocardiography is not and is at the discretion of the referring physician, usually only employed if the patient has a previous history of IHD or problems such as hypotension during dialysis.

Another weakness of this study was the relatively small number of patients who underwent coronary angiography. Due to both ethical and risk/benefit considerations, it was not possible to perform QCA on all patients entering the study. This meant that determination of the predictors of CAD in this population was not possible and conclusions regarding independent predictive power with regard to prognosis difficult. However, the main reason for including angiographic data was to validate the use of CMR imaging using the technique of LGCE in this population. It has already been established in other patients groups that the pattern of LGCE can differentiate NICM from ICM. In this study the typical pattern of LGCE found in ICM also was found to correspond with CAD at QCA. Again, our group has since reported on a larger population of patients undergoing CMR with LGCE and QCA.

Finally, the use of the West of Scotland renal database for follow-up meant that only data on all cause mortality could be collected. It was not possible to separate mortality into all-cause and CV mortality or to accurately monitor CV morbidity. Therefore, analysis specifically regarding CV morbidity and mortality was not possible.

10.4 Implications of the Study

The so called 'epidemic' of CVD in patients with progressive renal failure continues to account for the majority of morbidity and mortality observed in this population and after a shortage of donated renal allografts, is the biggest danger to life for patients awaiting renal transplantation. If the current demand for renal transplantation continues to rise, patients will wait longer for a renal transplant at a time in their lives when CV risk is more than 20 times that of the general population and therefore the early prevention, detection and treatment of CVD in patients awaiting renal transplantation is mandatory to improve survival for patients and to maximise the benefits of a subsequent renal transplant.

The aim of this study was to define the prevalence and pattern of LV abnormalities in a population of patients either already awaiting transplant or undergoing assessment for future transplantation, using the current standard of reference for the quantification of LV mass, volumes and function, CMR. In addition, the current practices for the primary and secondary prevention of CVD were examined as well as the current methods of identifying CAD in this population and the relationship of uraemic cardiomyopathy to CAD was explored using CMR imaging with LGCE. The implications of this study, possible action points and areas identified for future studies in this population are as follows;

- Both the primary and secondary prevention of CVD in this population could be better implemented. The prevalence of reversible risk factors such as hypertension and hyperlipidaemia were high and the prescription of cardioprotective medication low. The prescription rate of aspirin, statins, beta-

blockers and ACEI's was also low in 'higher risk' groups such as those with a history of IHD or diabetes. Strategies to improve the early identification and treatment of standard CV risk factors are required in this population in addition to a more aggressive approach to the implementation of secondary prevention.

- The predominant pattern of uraemic cardiomyopathy in this population is concentric LVH, which is determined by hypertension, volume overload and diabetes but not by anaemia. Future studies targeting regression of LVH in this population may be better served by treating hypertension with the prescription of medication or via strict control of volume status with differing dialysis regimes, rather than treating anaemia.
- The second main type of uraemic cardiomyopathy in this population is ICM rather than eccentric cardiomyopathy and IHD is closely associated with LVDil and LVSD. A finding of either of these LV abnormalities should precipitate careful investigation for underlying CAD but ideally CAD should be identified before the onset of adverse remodelling. CMR may be best equipped to study trials targeting reverse remodelling in this population. For example 30 patients would be required to detect a change of 3% in EF or 25mls in EDV in a trial studying active versus placebo medication, compared to 240 patients if using echocardiography.
- Patients with initially 'normal' left ventricles at baseline screening are at risk of developing abnormal ventricles via evolution of concentric LVH. This finding suggests these patients remain exposed to casual risk factors associated with LVH, such as hypertension, and as such, standard CV risk factors such as

hypertension should be aggressively treated in all patients. Furthermore, regular reassessment of LV abnormalities and CV risk in patients already placed on the transplant waiting list may be beneficial.

- The currently used non-invasive methods of detecting obstructive CAD in this population are unsatisfactory and with both the increase in choice and the improvements in technology associated with non-invasive imaging in the current era further study is warranted. It may be that a combination of functional and anatomical non-invasive imaging modalities is better suited for the detection of CAD in patients with ESRF.
- A high level of BNP was found to be an independent predictor of outcome for patients undergoing assessment for renal transplantation. BNP is easily measured in the setting of a clinic visit and may prove to be a useful addition to risk assessment in this population. Further studies are required both to verify our findings and assess whether lowering BNP levels in parallel with attempts to modify cardiac risk are associated with an improvement in prognosis.

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Glossary

ACEI- angiotensinogen converting enzyme inhibitor

ACS- acute coronary syndrome

AMI- acute myocardial infarction

ANP- atrial natriuretic peptide

APD- ambulatory peritoneal dialysis

ARIC study- Atherosclerosis Risk in Communities study

ASE- American Society of Echocardiography

BNP- brain natriuretis peptide

BP- blood pressure

BSA- body surface area

CABG- coronary artery bypass grafting

CAD- coronary artery disease

CAPD- continuous ambulatory peritoneal dialysis

CBD- cerebrovascular disease

CHF- 'congestive' heart failure

CHOIR- Correction of Hemoglobin and Outcomes in Renal Insufficiency trial

CI- confidence interval

CMR- cardiovascular magnetic resonance imaging

CNP- C-type natriuretic peptide

CO- cardiac output

COURAGE- Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation trial

CREATE- Cardiovascular Risk reduction by Early Anemia Treatment EPO trial

CRF- chronic renal failure

CRP- C reactive protein

CV- cardiovascular

CVD- cardiovascular disease

DSE- dobutamine stress echocardiography

ECG- electrocardiogram

ED- end-diastole

EDV- end-diastolic volume

EF- ejection fraction

ES- end-systole

ESRF- end stage renal failure

ESV- end-systolic volume

ETT- exercise tolerance testing

FFR- fractional flow reserve

FLASH- fast low angle shot

FoV- field of view

FS- fractional shortening

Gd-DTPA- gadolinium

GFR- glomerular filtration rate

HLA- horizontal long axis

ICM- ischaemic cardiomyopathy

IHD- ischaemic heart disease

IVS- interventricular septum

IVSTD- interventricular septum thickness in diastole

LGCE- late gadolinium contrast enhancement

LV- left ventricular

LVDil- left ventricular dilation

LVESD- left ventricular end systolic diameter

LVH- left ventricular hypertrophy

LVIDD- left ventricular internal diastolic diameter

LVMI- left ventricular mass index

LVSD- left ventricular systolic dysfunction

MET- metabolic equivalent of work

MHRA- Medicine and Healthcare products Regulatory Agency

NICM- non-ischaemic cardiomyopathy

NPR-C- natriuretic peptide receptor C

NPV- negative predictive value

NT-pro ANP- N- terminal pro atrial natriuretic peptide

NT-pro BNP- N-terminal pro brain natriuretic peptide

PCI- percutaneous intervention

PD- peritoneal dialysis

PET- positron emission tomography

PVD- peripheral vascular disease

PWTD- posterior wall thickness in diastole

QCA- quantitative coronary angiography

RR- relative risk

RRT- renal replacement therapy

SA- short axis

SD- standard deviation

SEE- standard error of estimation

SPECT- single photon emission computed tomography

SSFP- steady state free precession

STICH- Surgical Treatment for IsChaemic Heart failure trial

SV- stroke volume

SVR- systemic vascular resistance

TE- echo time

TR- repetition time

TRUE FISP- true fast imaging with steady state free precession

UK- United Kingdom

UK-HARP- United Kingdom Heart And Renal Protection study

US- United States of America

USRDS- United States Renal Data Service

VLA- vertical long axis

NORTH GLASGOW UNIVERSITY HOSPITALS NHS TRUST

THE WEST ETHICAL COMMITTEE

APPLICATION TO THE ETHICAL COMMITTEE FOR APPROVAL OF A CLINICAL RESEARCH PROJECT

Please read these guidelines before completing the proforma. You are also advised to refer to the document "Working with your Ethics Committee". *

1. One typed copy of this application must be submitted to Secretary, West Ethics Committee, Western Infirmary, **no later than 4pm on the Monday two weeks preceding the meeting of the Committee: the Committee meets on the first and third Tuesday of each month.** Late arriving protocols will not be considered until the next meeting.

2. All of the numbered headings must be addressed. Protocols must be presented in a concise manner with additional pages only being used if absolutely essential. Protocols presented in any other format or which deviate substantially from our guidelines in Working with your Ethics Committee will not be considered.

3. All investigators must sign the supporting Declaration Section 10). Copies of the complete Declaration of Helsinki are available from the Secretary West Ethics Committee. The principal investigator must complete Section 11 if the research project involves participation of healthy volunteers. Copies of the Report "Research on Healthy Volunteers", Royal College of Physicians of London, are available from the Administrator's office.

4 A patient/volunteer consent form must accompany all protocols and must pay heed to the advice given by the Committee on the inclusion of certain standard phrases.

5. The investigators must not recruit medical and nursing students to participate as research volunteers.

6. Protocols will fall from the agenda if information is not forthcoming within 3 months of requests being made by the Committee.

7. **Grants/Charges:** **See Attached Sheet**

Company ? **Charity ?** **Non-funded ?**

8. Is this Project Multi-centred i.e. taking place in 5 or more UK centres **? Yes ? No**

1. Brief Title of Project:

The detection of asymptomatic myocardial infarction in patients with chronic renal failure

2. Name, Grade and Personal Qualifications of Investigators.

Dr. Nicola Johnston, MB ChB, MRCP, Clinical Research Fellow
Dr. Alan Jardine, Bsc, MD, FRCP, Senior Lecturer in Nephrology
Professor Henry Dargie, MB ChB, FRCP, FRSE Consultant Cardiologist

Approved by: (If none of the investigators is a Consultant in the appropriate department)

Signature of approving Consultant

** Copies should be available in your department and the hospital libraries. Further copies can be obtained from the West Ethics Committee Secretary*

Ethi Comm use c

3. **Purpose of Study: (Please outline the background of the work, what information you hope to obtain and what you believe will be benefit to the patient and/or to medical science)**

Cardiovascular disease is the most common cause of death in patients with chronic renal failure, including those who have had a successful renal transplant, and accounts for over 40% of deaths in these patients. The age and sex adjusted risk of cardiovascular disease in this population is 10-20 times that of the general population and when the cause of renal failure is secondary to diabetes the risk of cardiovascular disease is 50 times that of the general population.

Non-invasive assessment in this patient population is difficult. Many patients, especially diabetics, do not have the classical symptoms of ischaemic heart disease due to poor exercise tolerance and for the same reason investigation such as exercise tolerance testing often provide unsatisfactory results. Resting ECG's in this population are often abnormal and ETT results are difficult to interpret even if the patient can exercise adequately. Other non-invasive assessment is available using stress perfusion but this exposes the patient to small doses of radioactive material.

Cardiovascular magnetic resonance provides a non-invasive method of measuring previous myocardial infarction. A contrast agent (gadolinium) is injected into the patient's vein and passes through the blood stream. Once it reaches the heart it diffuses through the myocardium. It diffuses through normal heart muscle very quickly. If, however there has been any previous damage from a myocardial infarction, however small, the contrast has delayed diffusion through this damaged tissue and has "delayed enhancement" of the contrast which is picked up by scanning the patient's heart around 15 minutes after injection. This can then be measured to estimate the territory of the myocardial infarction and the size of the myocardial infarction. The contrast agent used is

neither radioactive nor nephrotoxic and has proven to be at least as accurate as nuclear scanning in detecting myocardial infarction.

In this study we plan to carry out cardiovascular magnetic resonance utilising the method of late enhancement in high-risk patients with end-stage renal failure considered for renal transplant. These would be patients who are diabetic or who have evidence of left ventricular dysfunction or hypertrophy (the strongest predictive indicators of cardiac death in this patient group) on echocardiography and no previous history of myocardial infarction. We will also include 10 controls from the same population of patients with end-stage renal failure who are assessed for renal transplantation who have normal echocardiograms of their hearts for comparison. From the information gained we will be able to detect non-invasively the proportion of patients in this high-risk group who have in the past had a myocardial infarction and determine the association with standard cardiovascular risk factors. This would enable us to better identify these patients non-invasively in the future and in those patients in which previous myocardial infarction is identified the appropriate secondary preventative treatment can be instituted such as aspirin and statins as well as appropriate cardiology referral

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4. **<u>Details of Procedure</u>: (Explain how the study will be executed including details of recruitment, treatment allocation, procedures undertaken and study visits).**

All new patients at the Transplant Assessment Clinic at the Western Infirmary Glasgow who attend for routine cardiovascular screening (this includes ECG, ETT, echocardiogram and history taking for standard cardiovascular risk factors and cardiovascular physical examination) and who are diabetic or have left ventricular dysfunction or hypertrophy, diagnosed by echocardiography, but no previous history of myocardial infarction will be invited to participate. All patients who agree to participate will undergo the following;

1. Clinical evaluation (case note review, interview, examination and questionnaire) to determine history of cardiac symptoms and assess for standard cardiovascular risk factors.
2. ECG to look for evidence of previous ischaemic heart disease and assess for LVH.
3. Cardiovascular Magnetic Resonance to assess left ventricular anatomy, mass and function and using late enhancement with gadolinium to assess the presence and extent of previous myocardial infarction.
4. Blood tests. Blood will be analysed and drawn for full blood count, lipids, glucose and BNP (a neurohormone)

Following this, those patients who have been shown to have a myocardial infarction will be referred to Professor Dargie's cardiology clinic for appropriate further investigation and management.

This process will involve a visit that should last one hour and thirty minutes. The clinical evaluation will take around thirty minutes and the cardiovascular magnetic resonance scan will take around 50 minutes. After analysis of the scans the patient may be recalled to discuss the results, if they are positive, and referred to the cardiology clinic.

If the patient has a positive scan, and fulfilled the required criteria on the treadmill and had a satisfactory echocardiogram they would still be added to the transplant register. Only if they had significant ECG changes at treadmill, a severely impaired ventricle on echo or a reversible defect on thallium scanning (if they cannot complete the treadmill time) would there be a delay to being added to the transplant register. This is the current workup for transplant candidates in this hospital.

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5. **<u>Facilities and Personnel to support the work</u> : Indicate here how the facilities and personnel you have available will enable the project to be adequately executed).**

Recruitment and consent of patients will be performed by Dr. Nicola Johnston who co-ordinates cardiovascular screening at the renal transplant clinic.

Screening will be performed in the Clinical Research Initiative (CRI) of the Western Infirmary by CRI staff using existing equipment. The cardiovascular magnetic resonance scans will be performed in the CRI scanner by existing staff (Miss T Steedman). Analysis of the scans will be performed by Dr. Nicola Johnston. Analysis of non-routine blood samples will be performed by Dr. Ian Morton in the Department of Medicine lab in the Western Infirmary. Decision to refer to cardiology clinic will be taken by Dr. Nicola Johnston and Professor Henry Dargie.

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6. **<u>Patient/Volunteers</u>: (Please indicate how patients and/or volunteers are chosen giving the numbers chosen and justification for these numbers with power calculations where appropriate. Entry and exclusion criteria should be clearly stated.**
Particular regard should be paid to the status of women of childbearing age.

All patients seen at the Transplant Assessment Clinic who are diabetic or have evidence of left ventricular dysfunction or hypertrophy, with no previous history of myocardial infarction will be invited to attend. Women of childbearing age will be invited to take part but will only undergo cardiovascular magnetic resonance scanning after a negative pregnancy test. Pregnancy or breast feeding at the time of recruitment are exclusion criteria as well as any of the usual contra-indications to cardiovascular magnetic resonance scanning e.g. permanent pacemaker, aneurysm clips etc.

Ten "normal" controls will be recruited from the transplant waiting list who have normal echocardiograms. This is to help clarify the relationship between left ventricular abnormalities and previous myocardial infarction in patients with end-stage renal disease. This number is calculated from that used in similar studies and using standard deviation of inter-observer variability for cardiovascular magnetic resonance imaging and it is estimated that 70 patients will require to be studied with this method of late enhancement.

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7. **Drugs, dosages and non-standard products (Please include all drugs. If a new drug is to be used a copy of the Clinical Trials Certificate or Clinical Trials Exemption Certification from the Committee on Safety of Medicines must be attached).**

Gadolinium-DTPA

Gadolinium is a metallic chemical element chelated to a substance called diethylene triaminepentaacetic acid (DTPA) for clinical use (Gd-DTPA). Gd-DPTA is a paramagnetic agent and increases the relaxation rate of surrounding protons thereby shortening the T1 relaxation times and increasing the signal density on cardiac MRI (CMR) images. Gadolinium is already in routine clinical use.

Dosages

An intravenous bolus via a peripheral line. It will be given as a bolus injection of 7-10 mls by hand. Each injection will be 0.05 mmol/Kg body weight. The median lethal dose is 10 mmol/Kg, which is 50-100 times the diagnostic dose.

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8. **Safety: (Please state briefly the known pharmacology of the drugs used indicating side effects and toxicity, together with hazards of any invasive procedure performed). The minimum information would be that contained in the British Formulary**

Gadolinium

Pharmacokinetics

Half life 1.6 hours.

Contraindications

None

Cautions

Patients with a history of thrombotic syndromes. Patients with a history of sickle cell anaemia and other haemoglobiopathies such as haemolytic anaemia. Patients with severe renal or hepatic impairment. Patients with a known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders

Side effects

The most common noted adverse event is headache with an incidence of 4.8%. The majority of headaches are transient and of mild to moderate severity. Nausea is the second most common adverse event at around 2.7%. Injection site coldness/localised coldness is the third most common adverse event at 2.3%. The incidence of anaphylactic adverse reactions is extremely rare (1 in 100,000 doses). There is no nephrotoxicity even at high doses, which is particularly relevant in this population.

Precautions – general

As with other injectable products, cases of phlebitis and thrombophlebitis have been reported. Patency and integrity of the intravenous line will be determined before administration. As with other intravenous injections, appropriate surveillance of the dosing limb for the development of local injection site reactions following administration of the drug will be carried out.

Gadolinium is renally excreted, hence the caution for those patients with severe renal impairment. However, all of these patients are on dialysis, whether it be peritoneal dialysis or haemodialysis and therefore the gadolinium will be effectively removed by dialysis causing minimal increased risk of side-effects

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9. **Radioactive Substances: (If radioisotopes are to used, details of premises clearance by Radiation Protection Officer should be given and certificate of registration with the DHSS must be attached. The approximate dose of radioactivity administration should be stated).**

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10. **<u>Grant or Financial Support</u> (<u>ALL</u> sources of support for the work should be stated including details of all payments to be made to investigators, patients and healthy volunteers.**

The study will be funded by the Clinical Research Initiative of the Western Infirmary Glasgow. Dr. Nicola Johnston is supported by a British Heart Foundation Junior Research Fellowship

11. **<u>Supporting Declaration</u> (<u>ALL</u> named investigators must sign).**

"I certify that I have considered the declaration of Helsinki and this protocol adheres to the principles contained therein".

12. **<u>Research on Healthy Volunteers</u> (Must be signed by the principal investigator/s).**

"I certify that I have considered the report of the Royal College of Physicians and this protocol adheres to the principles contained in that report. I confirm that healthily volunteers will have their legal position fully explained to them, particularly in respect of the ability to claim for damages should anything untoward occur to them as a result of their participation in research trails".

Signature.....

Designation.....

Date.....

Approved by the Ethical Committee

Date.....

THIS SHEET HAS BEEN APPROVED BY THE WEST ETHICS COMMITTEE

INFORMATION SHEET FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Brief Title of Project

The detection of asymptomatic myocardial infarction in patients with chronic renal failure

Patient's Summary (Purpose of study, nature of procedure, discomfort and possible risks in terms which the patient or volunteer can understand).

You are invited to take part in a study looking at a very sensitive technique to detect any previous damage to the heart muscle. You have been selected because patients with kidney disease have a much higher risk of heart disease and problems with the circulation than the rest of the general population. Often it is difficult to fully assess heart problems in patients with kidney failure as some patients cannot exercise easily and therefore heart symptoms such as breathlessness and chest pain may remain undetected or silent. Also, the usual way in which we test the heart such as walking on a treadmill can often be difficult for patients with kidney disease as they often have other problems such as arthritis.

The study will involve a new test for heart disease. We will ask you questions about your health, examine you and perform an ECG, which is a simple recording of the heart done through leads attached to your chest by sticky labels and taking around 2 minutes to complete. We will then carry out a special scan called a cardiac MRI scan. Finally we will take a blood test. To do this we will insert a very fine plastic tube, a little wider than a pin, into a vein in your arm and from this we will withdraw approximately 20ml of blood, (roughly around 3 dessert spoonfuls)

Cardiac MRI

This is a way of getting very detailed pictures of the heart without using X-rays. MRI instead uses a magnet, radio waves and a powerful computer to produce the pictures. Before the scan you will need to change into a gown as zips and metal fasteners can interfere with the pictures. The radiographer will ask you a list of questions to check if you have any metal in your body (either from surgery or from accidents involving metal). When you are being scanned you have to lie very still in the scanner. The machine is shaped like a tunnel and can be claustrophobic. When the scan is on, the machine will make a loud knocking noise. Headphones will be given to you and music can be played. You will be in contact with the radiographer who will be monitoring the whole process from outwith the room. You will be given an emergency buzzer and very quickly can be taken out of the scanner should it be necessary. Each scan will typically require you to hold your breath for around 8 seconds. The whole exam may last between 30 and 60 minutes. About half way through the scan we will inject a small amount of

dye into a vein in your arm through a fine plastic tube. This "dye" is called gadolinium and provides greater contrast between normal and abnormal tissue. It looks like clear water and has been used for years in adults and children without any serious complications in thousands of patients. A few side effects such as headache, nausea and local burning can occur. Very rarely (less than one in a thousand) patients are allergic to gadolinium. These side effects may be more common in dialysis patients as the dye is removed from the body by the kidney and will therefore be removed during dialysis and may be in the body slightly longer than usual. Gadolinium does not affect the function of the kidney.

The results of these tests will be analysed. If the test shows up any abnormality we will discuss the results with you and may advise you to have further heart tests or to start new medication. **If the tests do show up abnormalities this may result in a delay in joining the kidney transplant waiting list whilst these abnormalities are investigated**.

Taking part in this study may not directly benefit you, although we may discover and be able to treat silent heart problems, which you could have. It is designed to help us assess and treat kidney patients better in the future. If you are willing to take part we will inform your GP and explain the nature of the study to him or her. Should you choose to drop out or not take part, you can do this at any time, without giving a reason and this will not affect your routine care in any way.
If you wish to discuss any aspects of the study please contact **Dr. N Johnston at the Western Infirmary, Glasgow. (Telephone 0141 211 2637, or-email njohnstoncri@yahoo.com)**

N.B. Pregnancy would be a contraindication to taking part in this study and therefore if you are a woman of childbearing age we will perform a pregnancy test prior to any procedures and if you are pregnant or breastfeeding we would not ask you to take part in the study.

WEST ETHICS COMMITTEE

FORM OF CONSENT FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project: The detection of silent myocardial infarction in patients with chronic renal failure.

By signing this form you give consent to your participation in the project whose title is at the top of this page. You should have been given a complete explanation of the project to your satisfaction and have been given the opportunity to ask questions. You should have been given a copy of the patient information sheet approved by the West Ethics Committee to read and to keep. Even though you have agreed to take part in the research procedures you may withdraw this consent at any time without the need to explain why and without any prejudice to your care.

Consent:

I,.....(PRINT)

of.....

give my consent to the research procedures above, the nature, purpose and possible consequences
of which have been described to me

by.....

Patient's signature.....Date.....

Doctor's signature.....

Publications containing work undertaken for this thesis

PB Mark, **N Johnston**, BA Groenning, JE Foster, KG Blyth, TN Martin, T Steedman, HJ Dargie, AG Jardine. Redefinition of uremic cardiomyopathy by contrast enhanced cardiac magnetic resonance imaging. *Kidney International (2006),69,1839-1845*

Oral presentations to Learned Societies containing work undertaken for this thesis

N Johnston, G Stewart, A Jardine, H Dargie. Evaluation of the uraemic heart using Cardiovascular Magnetic Resonance. **British Cardiac Society**; May 2002 (Harrogate).

N Johnston, T Steedman, J Foster, A Jardine, HJ Dargie. The detection of asymptomatic myocardial infarction in patients awaiting renal transplantation using Cardiovascular Magnetic Resonance Imaging- **British Cardiac Society**; April 2003 (Glasgow).

Poster presentations to Learned Societies containing work undertaken for this thesis

N Johnston, T Steedman, RSC Rodger, A Jardine, H Dargie. Defining the relationship between Ischaemic Heart Disease and Uraemic Cardiomyopathy using Cardiovascular Magnetic Resonance. **The Renal Association**; October 2002 (London).

N Johnston, T Steedman, J Foster, J Morton, AG Jardine, HJ Dargie. The potential use of BNP as a screening tool in the cardiovascular risk assessment of patients felt suitable for renal transplantation. **European Society of Cardiology;** Sept 2007, Vienna